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(54) Title: SUBSTITUTED DI(HYDROXY/ALKOXY)SILICON PHTHALOCYANINES AND THEIR USES

(57) Abstract: This invention relates to certain substituted di(hydroxy/alkoxy)silicon phthalocyanines and certain uses thereof, in particular their uses in photodynamic therapy and in photodiagnostics.

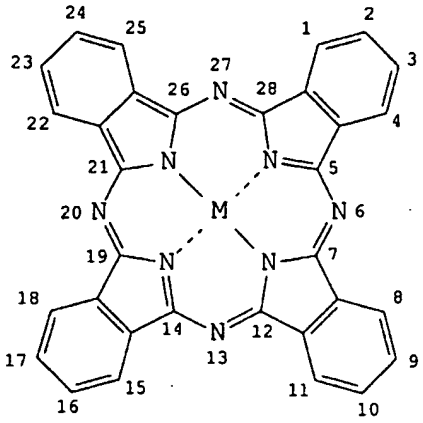
Substituted Di(hydroxy/alkoxy)silicon Phthalocyanines and Their Uses

Field of the invention

This invention relates to certain substituted di(hydroxy/alkoxy)silicon phthalocyanines and certain uses thereof, in particular their uses in photodynamic therapy and in photodiagnostics.

Background of the invention

In recent years significant research has been conducted into the synthesis of substituted phthalocyanines. This has been driven in part by the fact that substituted phthalocyanines show a multitude of desirable properties and are thus useful for a wide variety of applications. The desirable properties of substituted phthalocyanines can often be tuned by manipulation of the substituents on the ring system. In general these substituents fall into two categories, the so-called peripheral (2, 3, 9, 10, 16, 17, 23, 24) and the non-peripheral (1, 4, 8, 11, 15, 18, 22, 25) substituents, as shown in Scheme 1.



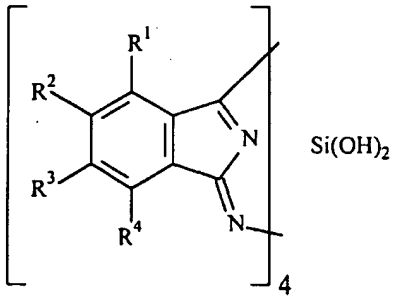
Scheme 1

The central M is a metal or metal compound or two hydrogen atoms, one hydrogen being bonded to each of the two bonding nitrogen atoms. The phthalocyanines most commonly synthesised and investigated, are metal free (i.e. M is two hydrogens) or metallated with M being Zn, Cu, Ni, Co, Fe, Mn, Mg and Pb. Di(hydroxy/alkoxy)silicon phthalocyanines have been synthesised very rarely and their properties have to date not been thoroughly investigated and fully appreciated. The fact that

di(hydroxy/alkoxy)silicon phthalocyanines substituted on the phthalocyanine ring as claimed in the present invention show (a) a higher solubility in a greater range of solvents, notably in methanol and ethanol, (b) a higher extinction coefficient, and (c) improved biological effects, when compared to, for example, the corresponding substituted zinc phthalocyanines, was hitherto unknown, such that their usefulness in the photodynamic therapy and in photodiagnostics has thus far not been recognised.

In particular three groups, Mitsui Toatsu Chemicals Inc., Yamamoto Chemicals Inc. and Kenney *et al.*, have disclosed various phthalocyanines, including some silicon centred phthalocyanines. In the late eighties and early nineties, Mitsui Toatsu Chemicals Inc. and Yamamoto Chemicals Inc. filed the following patent applications relating to infrared absorbing phthalocyanines.

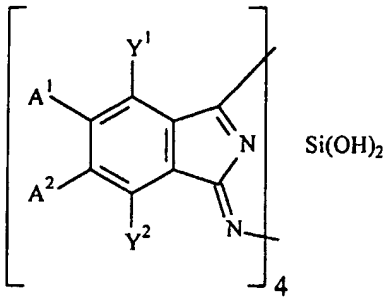
EP-0 337 209 (Mitsui Toatsu Chemicals Inc. and Yamamoto Chemicals Inc.) describes alkylphthalocyanines which are near-infrared absorbers such that they may usefully be employed in optical recording media, near-infrared absorption filters and liquid crystal display devices. Photodynamic therapy is not mentioned. The phthalocyanines may be metal free or metallated. $Si(OH)_2$ and $Si(OR)_2$, wherein R may be alkyl, are listed amongst a large number of possible central metals and metal compounds. Out of 79 example compounds, one has a central $Si(OH)_2$, namely:



wherein $R^1 = -CH_2C_6H_5$, $R^2 = -CH_2C_6H_5$, $R^3 = -CH_2C_6H_5$ and $R^4 = -CH_2C_6H_5$.

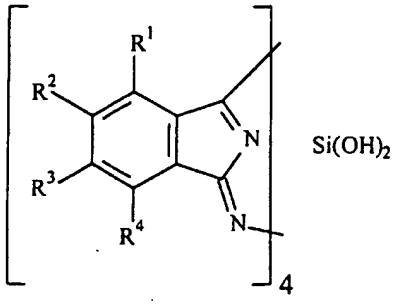
EP-0 373 643 (Mitsui Toatsu Chemicals Inc. and Yamamoto Chemicals Inc.) describes phthalocyanines which are near-infrared absorbers which may usefully be employed in display/recording materials. Photodynamic therapy is not mentioned. The phthalocyanines may be metal free or metallated. $Si(OH)_2$ and $Si(OR)_2$, wherein R may be

alkyl, are mentioned amongst a large number of possible central metals and metal compounds. Out of 103 example compounds, three have a central $Si(OH)_2$, namely:



wherein $Y^1 = -O^iC_5H_{11}$, $Y^2 = -O^iC_4H_9$, $A^1 = -CH_3$ and $A^2 = -CH_3$, or
$Y^1 = -O^nC_5H_{11}$, $Y^2 = -O^nC_5H_{11}$, $A^1 = -SC_6H_5$ and $A^2 = -SC_6H_5$, or
$Y^1 = -OC_8H_{17}$, $Y^2 = -OC_8H_{17}$, $A^1 = -SC_6H_5$ and $A^2 = -SC_6H_5$.

EP-0 519 423 (Mitsui Toatsu Chemicals Inc. and Yamamoto Chemicals Inc.) describes metallated phthalocyanines useful for the fabrication of colour filters; again photodynamic therapy is not mentioned. $Si(OH)_2$ is mentioned amongst a large number of possible central metals and metal compounds. Out of 124 example compounds, one has a central $Si(OH)_2$, namely:



wherein $R^1 = -(SCH_2CH_2)_3\text{-}N(CH_2CH_3)_2$, $R^2 = -O\text{-}C_6H_4\text{-}p\text{-}Cl$, $R^3 = -O\text{-}C_6H_4\text{-}p\text{-}Cl$ and $R^4 = -Cl$.

Thus, although the disclosures by Mitsui Toatsu Chemicals Inc. and Yamamoto Chemicals Inc. describe five silicon dihydroxide phthalocyanines, Mitsui Toatsu Chemicals Inc. and Yamamoto Chemicals Inc. were unaware of the fact that the di(hydroxy/alkoxy)silicon phthalocyanines as claimed in the present application are useful in photodynamic therapy.

Throughout the eighties and nineties, Kenney *et al.* published various papers and patent applications relating to phthalocyanines, some of which were thought to be potentially useful in photodynamic therapy.

Kenney *et al.* (J. Am. Chem. Soc., 1984, vol. 106, pages 7404-7410) describe the synthesis, electrochemistry and electrogenerated chemiluminescence of $PcSi[OSi(n\text{-}C_6H_{13})_3]_2$, its dimer $[(n\text{-}C_6H_{13})_3Si](OSiPc)_2[OSi(n\text{-}C_6H_{13})_3]$ and its naphthalocyanine analogue $NcSi[OSi(n\text{-}C_6H_{13})_3]_2$, which were prepared as follows (Pc meaning phthalocyanine and Nc meaning naphthalocyanine):

$$PcSi[OH]_2 + ClSi(n\text{-}C_6H_{13})_3 \rightarrow PcSi[OSi(n\text{-}C_6H_{13})_3]_2$$

$$NcSi[OH]_2 + ClSi(n\text{-}C_6H_{13})_3 \rightarrow NcSi[OSi(n\text{-}C_6H_{13})_3]_2$$

$$PcSi[OH]_2 + PcSiCl_2 + N(n\text{-}C_6H_{13})_3 \rightarrow [(n\text{-}C_6H_{13})_3SiO]PcSiOPcSi[OSi(n\text{-}C_6H_{13})_3]$$

It is said that the presence of the trialkylsiloxy groups on the central Si atom leads to relatively high solubility and that the solubility of naphthalocyanines is directly associated with the size and nature of their axial ligands. No mention of photodynamic therapy is made.

Kenney *et al.* (J. Am. Chem. Soc., 1988, vol. 110, pages 7926-7930) prepared $NcSi[OSi(C_6H_{13})_3]_2$ and conducted energy transfer experiments showing that energy transfer from the triplet state of $NcSi[OSi(C_6H_{13})_3]_2$ to O_2 to produce singlet oxygen is a reversible reaction, which makes $NcSi[OSi(C_6H_{13})_3]_2$ potentially useful as a photosensitizer in the photodynamic therapy of tumours.

Kenney *et al.* (SPIE, Photodynamic Therapy: Mechanisms II, 1990, vol 1203, pages 224-232) prepared various silicon, germanium, tin, aluminum, gallium, palladium and ruthenium naphthalocyanines. In particular, the following syntheses of silicon naphthalocyanines are disclosed:

$NcSiCl_2 + NaO\text{-}n\text{-}C_8H_{17} \rightarrow NcSi[O\text{-}n\text{-}C_8H_{17}]_2$

$NcSi[O\text{-}n\text{-}C_8H_{17}]_2 + HOSi(n\text{-}C_6H_{13})_3 \rightarrow NcSi[OSi(n\text{-}C_6H_{13})_3]_2$

$NcSi(OH)_2 + ClSi(n\text{-}C_6H_{13})_3 \rightarrow NcSi[OSi(n\text{-}C_6H_{13})_3]_2$

$NcSiCl_2 + NaO\text{-}n\text{-}C_8H_{17} \rightarrow NcSi[O\text{-}n\text{-}C_8H_{17}]_2$

$NcSi[O\text{-}n\text{-}C_8H_{17}]_2 + HOSi(i\text{-}C_4H_9)_2(n\text{-}C_{18}H_{37}) \rightarrow NcSi[OSi(i\text{-}C_4H_9)_2(n\text{-}C_{18}H_{37})]_2$

$Nc(2/3\text{-}Cl)_4SiCl_2 + NaO\text{-}n\text{-}C_8H_{17} \rightarrow Nc(2/3\text{-}Cl)_4Si[O\text{-}n\text{-}C_8H_{17}]_2$

$Nc(2/3\text{-}Cl)_4Si[O\text{-}n\text{-}C_8H_{17}]_2 + HOSi(n\text{-}C_6H_{13})_3 \rightarrow Nc(2/3\text{-}Cl)_4Si[OSi(n\text{-}C_6H_{13})_3]_2$

$Nc(2/3\text{-}Br)_4SiCl_2 + NaO\text{-}n\text{-}C_8H_{17} \rightarrow Nc(2/3\text{-}Br)_4Si[O\text{-}n\text{-}C_8H_{17}]_2$

$Nc(2/3\text{-}Br)_4Si[O\text{-}n\text{-}C_8H_{17}]_2 + HOSi(n\text{-}C_6H_{13})_3 \rightarrow Nc(2/3\text{-}Br)_4Si[OSi(n\text{-}C_6H_{13})_3]_2$

It was found that the solubilities of the compounds are highly correlated with the types of axial ligands present. Of the silicon naphthalocyanines, in particular $SiNc[OSi(i\text{-}C_4H_9)_2(n\text{-}C_{18}H_{37})]_2$ was thought to be potentially useful as photodynamic sensitizer.

WO 92/01753 (Kenney *et al.*) describes aluminum and silicon phthalocyanines having at least one substituted amine or quaternary ammonium axial ligand attached to the central aluminum or silicon atom. Two aluminum and four silicon phthalocyanines were thought to be potentially useful in the treatment of cancer through photosensitisation. The four silicon phthalocyanines were synthesised as follows:

$PcSi[CH_3][OH] + CH_3\text{-}OSi(CH_3)_2(CH_2)_3N(CH_3)_2 \rightarrow$
$PcSi[CH_3][OSi(CH_3)_2(CH_2)_3N(CH_3)_2]$

$PcSi[CH_3][OSi(CH_3)_2(CH_2)_3N(CH_3)_2] + H_2O \rightarrow PcSi[OH][OSi(CH_3)_2(CH_2)_3N(CH_3)_2]$

$PcSi[OH][OSi(CH_3)_2(CH_2)_3N(CH_3)_2] + CH_3I \rightarrow PcSi[OH][OSi(CH_3)_2(CH_2)_3N(CH_3)_3{}^{+}I^{-}]$

$PcSi[OH]_2 + CH_3\text{-}OSi(CH_3)_2(CH_2)_3N(CH_3)_2 \rightarrow PcSi[OSi(CH_3)_2(CH_2)_3N(CH_3)_2]_2$

$PcSi[OSi(CH_3)_2(CH_2)_3N(CH_3)_2]_2 + CH_3I \rightarrow PcSi[OSi(CH_3)_2(CH_2)_3N(CH_3)_3{}^+I^-]_2$

Kenney *et al.* (Cancer Letters, 1992, vol. 65, pages 145-150) prepared $NcSi(O(CH_2CH_2O)_{\sim 44}CH_3)_2$, hoping that the use of axial ligands on the central silicon atom would render the phthalocyanine water soluble enough to make it useful as an *in vivo* photosensitizer, thereby avoiding having to introduce peripheral substituents, such as sulphonate or carboxylate groups, through laborious procedures which were said often to yield mixtures of isomeric compounds. However, pharmacokinetic and photodynamic experiments indicated that $NcSi(O(CH_2CH_2O)_{\sim 44}CH_3)_2$ has little tumour selectivity and essentially no phototherapeutic activity.

Kenney *et al.* (Inorg. Chem., 1992, vol. 31, pages 3371-3377) prepared various aluminum, gallium, silicon and tin naphthalocyanines and examined their photochemical properties. It was found that the nature of the axial ligands of a silicon naphthalocyanine can have a significant effect on its photoproperties. It was further found that $SiNc[OSi(i\text{-}C_4H_9)_2(n\text{-}C_{18}H_{37})]_2$ has a property set of interest for photodynamic therapy. The following syntheses of silicon naphthalocyanines are disclosed:

$NcSi(OH)_2 + n\text{-}C_8H_{17}\text{-}OH \rightarrow NcSi(O\text{-}n\text{-}C_8H_{17})_2$

$NcSi(O\text{-}n\text{-}C_8H_{17})_2 + 4\text{-}HOC_6H_4\text{-}CO_2H + CH_3(OCH_2CH_2)_3OH \rightarrow$
$NcSi[4\text{-}OC_6H_4\text{-}CO(OCH_2CH_2)_3OCH_3]_2$

$NcSi(O\text{-}n\text{-}C_8H_{17})_2 + n\text{-}C_{18}H_{37}(i\text{-}C_4H_9)_2\text{-}SiOH \rightarrow NcSi[OSi(i\text{-}C_4H_9)_2(n\text{-}C_{18}H_{37})]_2$

$NcSi(O\text{-}n\text{-}C_8H_{17})_2 + CH_3O_2C(CH_2)_{10}Si(CH_3)_2Cl \rightarrow NcSi[OSi(CH_3)_2(CH_2)_{10}CO_2CH_3]_2$

$NcSi(OH)_2 + CH_3(OCH_2CH_2)_nOH \rightarrow NcSi[(OCH_2CH_2)_{\sim 17 \text{ or } \sim 43}OCH_3)]_2$

$NcSi(OH)_2 + 4\text{-}H(OCH_2CH_2)_{\sim 26}OC_6H_4C(CH_3)_2\text{-}CH_2C(CH_3)_3 \rightarrow$
$NcSi[4\text{-}(OCH_2CH_2)_{\sim 26}OC_6H_4C(CH_3)_2\text{-}CH_2C(CH_3)_3]_2$

$NcSi(OH)_2 + n\text{-}C_{18}H_{37}(n\text{-}C_4H_9)_2SiCl \rightarrow NcSi[OSi(n\text{-}C_4H_9)_2(n\text{-}C_{18}H_{37})]_2$

$NcSi(2/3\text{-}Cl)_4Cl_2 + n\text{-}C_8H_{17}\text{-}OH \rightarrow NcSi(2/3\text{-}Cl)_4(O\text{-}n\text{-}C_8H_{17})_2$

$NcSi(2/3\text{-}Cl)_4(O\text{-}n\text{-}C_8H_{17})_2 + HCl \rightarrow NcSi(2/3\text{-}Cl)_4(OH)_2$

$NcSi(2/3\text{-}Br)_4Cl_2 + n\text{-}C_8H_{17}\text{-}OH \rightarrow NcSi(2/3\text{-}Br)_4(O\text{-}n\text{-}C_8H_{17})_2$

$NcSi(2/3\text{-}Br)_4(O\text{-}n\text{-}C_8H_{17})_2 + HCl \rightarrow NcSi(2/3\text{-}Br)_4(OH)_2$

Kenney *et al.* (Br. J. Cancer, 1990, vol. 62, pages 966-970; Photochemistry and Photobiology, 1994, vol. 59, no. 1, pages 66-72; and Photochemistry and Photobiology, 1994, vol. 59, no. 3, pages 362-365) prepared $NcSi[OSi(C(CH_3)_3)_2(C_{18}H_{37})]_2$ and performed pharmacokinetic and photodynamic experiments which indicated that $NcSi[OSi(C(CH_3)_3)_2(C_{18}H_{37})]_2$ may be an effective photosensitizer for photodynamic therapy of tumours in mice and rats.

WO 98/14521 (University Hospitals of Cleveland for Kenney *et al.*) describes the following two synthetic routes to silicon phthalocyanines having at least one silyloxy ligand attached to the central silicon atom. In particular $PcSi[OH][OSi(CH_3)_2(CH_2)_3N(CH_3)_2]$, $PcSi[OH][OSi(CH_3)_2(CH_2)_3I]$ and $PcSi[OSi(CH_3)_2(CH_2)_3I]_2$ are said to be useful as dyes and in photodynamic therapy.

$PcSi[OH]_2 + CH_3\text{-}OSi(CH_3)_2(CH_2)_3N(CH_3)_2 \rightarrow PcSi[OSi(CH_3)_2(CH_2)_3N(CH_3)_2]_2 \rightarrow$
$PcSi[O\text{-}COCCl_3][OSi(CH_3)_2(CH_2)_3N(CH_3)_2] \rightarrow PcSi[OH][OSi(CH_3)_2(CH_2)_3N(CH_3)_2]$

$PcSi[OH]_2 + CH_3\text{-}OSi(CH_3)_2(CH_2)_3I \rightarrow PcSi[OSi(CH_3)_2(CH_2)_3I]_2 \rightarrow$
$PcSi[O\text{-}COCCl_3][OSi(CH_3)_2(CH_2)_3I] \rightarrow PcSi[OH][OSi(CH_3)_2(CH_2)_3I] \rightarrow$
$PcSi[OH][OSi(CH_3)_2(CH_2)_3N(CH_3)_2]$

Kenney *et al.* (J. Am. Chem. Soc., 1998, vol. 117, pages 6029-6039) describe the following route to silicon phthalocyanines which entails insertion of a silicon compound into the metal-free macrocycle (wherein N means naphthalene derived and P means phthalonitrile derived).

$N_4P_0(OBu)_8 + HSiCl_3 + NBu_3 \rightarrow SiN_4P_0(OBu)_8(OH)_2$

$SiN_4P_0(OBu)_8(OH)_2 + ClSi(n\text{-}C_6H_{13})_3 + pyridine \rightarrow SiN_4P_0(OBu)_8(OSi(n\text{-}C_6H_{13})_3)_2$

$N_3P_1(OBu)_8 + HSiCl_3 + NBu_3 \rightarrow SiN_3P_1(OBu)_8(OH)_2$

$SiN_3P_1(OBu)_8(OH)_2 + ClSi(n\text{-}C_6H_{13})_3 + pyridine \rightarrow SiN_3P_1(OBu)_8(OSi(n\text{-}C_6H_{13})_3)_2$

$c\text{-}N_2P_2(OBu)_8 + HSiCl_3 + NBu_3 \rightarrow c\text{-}SiN_2P_2(OBu)_8(OH)_2$

$c\text{-}SiN_2P_2(OBu)_8(OH)_2 + ClSi(n\text{-}C_6H_{13})_3 + pyridine \rightarrow c\text{-}SiN_2P_2(OBu)_8(OSi(n\text{-}C_6H_{13})_3)_2$

$t\text{-}N_2P_2(OBu)_8 + HSiCl_3 + NBu_3 \rightarrow t\text{-}SiN_2P_2(OBu)_8(OH)_2$

$t\text{-}SiN_2P_2(OBu)_8(OH)_2 + ClSi(n\text{-}C_6H_{13})_3 + pyridine \rightarrow t\text{-}SiN_2P_2(OBu)_8(OSi(n\text{-}C_6H_{13})_3)_2$

$N_1P_3(OBu)_8 + HSiCl_3 + NBu_3 \rightarrow SiN_1P_3(OBu)_8(OH)_2$

$SiN_1P_3(OBu)_8(OH)_2 + ClSi(n\text{-}C_6H_{13})_3 + pyridine \rightarrow SiN_1P_3(OBu)_8(OSi(n\text{-}C_6H_{13})_3)_2$

$N_0P_4(OBu)_8 + HSiCl_3 + NBu_3 \rightarrow SiN_0P_4(OBu)_8(OH)_2$

$SiN_0P_4(OBu)_8(OH)_2 + ClSi(n\text{-}C_6H_{13})_3 + pyridine \rightarrow SiN_0P_4(OBu)_8(OSi(n\text{-}C_6H_{13})_3)_2$

Thus, six compounds of $SiN_xP_{4-x}(OBu)_8$, $SiN_xP_{4-x}(OBu)_8(OH)_2$ and $SiN_xP_{4-x}(OBu)_8(OSi(C_6H_{13})_3)_2$ respectively, wherein x varies between 0 and 4, were prepared. It was shown that c- and $t\text{-}SiN_2P_2(OBu)_8(OSi(C_6H_{13})_3)_2$ have photophysical properties that render them suitable as photosensitizers in the photodynamic therapy of tumours and as red or near-infrared light absorbers in optical data storage systems.

Thus, in some of their papers and patent applications Kenney *et al.* mention that the disclosed phthalocyanines may be useful in photodynamic therapy. All compounds highlighted by Kenney *et al.* as potentially useful in photodynamic therapy are silicon-centred phthalocyanines with at least one axial silyloxy ligand.

As is well known, unsubstituted silicon dihydroxide phthalocyanine ($PcSi(OH)_2$) is insoluble or has a low solubility in most solvents, and as indicated in various of Kenney's papers, the solubility of the phthalocyanines is directly related to the size and nature of the axial ligands. The solubility of a photodynamic agent is, of course, critically important for

its effectiveness. Thus, Kenney *et al.* render their silicon-centred phthalocyanines soluble by the introduction of at least one large axial silyloxy ligand. Kenney *et al.* indicate that they chose to introduce large axial ligands on the central silicon atom in order to avoid having to introduce substituents on the phthalocyanine ring, which is said to be a laborious procedure which often yields mixtures of isomeric compounds.

Indeed, the only silicon dihydroxide phthalocyanines disclosed by Kenney *et al.* are unsubstituted phthalocyanine ($Pc(OH)_2$) and naphthalocyanine ($Nc(OH)_2$), naphthalocyanines $NcSi(2/3\text{-}Cl)_4(OH)_2$ and $NcSi(2/3\text{-}Br)_4(OH)_2$ with the simple substitution pattern of four peripheral chlorine or bromine atoms, and mixed phthalocyanine/naphthalocyanines $SiN_xP_{4-x}(OBu)_8(OH)_2$ with the simple substitution pattern of eight non-peripheral butoxy groups. The reason Kenney *et al.* do not disclose silicon dihydroxide phthalocyanines with more complex substitution patterns is, as outlined in the co-pending International patent application PCT/GB00/04708 hereby incorporated by reference, that a large variety of substituents cannot be introduced into the phthalocyanine ring by any prior art syntheses, because the functionality of many substituents is incompatible with the reaction conditions required by the prior art syntheses.

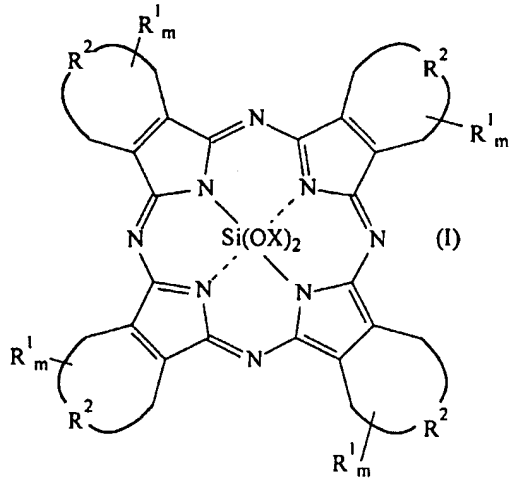
Very recently, Maree *et al.* (M.D. Maree, N. Kuznetsova and T. Nyokong, Journal of Photochemistry and Photobiology A: Chemistry, 2001, vol. 140, pages 117-125) prepared a series of silicon octaphenoxyphthalocyanines and studied their photostability and singlet oxygen quantum yields. One of the compounds prepared was silicon dihydroxide octaphenoxyphthalocyanine. Maree *et al.* concluded that the poor singlet oxygen quantum yield of this silicon dihydroxide phthalocyanine is due to its poor solubility in organic solvents, possibly caused by hydrogen bond attraction between the axial hydroxyl groups. This conclusion is based on the fact that intermolecular interactions between phthalocyanine rings, such as for example hydrogen bonds, result in decreased photochemical activity due to enhanced probability of radiationless decay of excited states. Thus, the results obtained by Maree *et al.* suggest that all silicon dihydroxide phthalocyanines will make poor photodynamic agents, because their poor solubility in organic solvents will give rise to poor quantum yields of singlet oxygen.

The other silicon octaphenoxyphthalocyanines prepared by Maree *et al.* give rise to promising singlet oxygen quantum yields due to their good solubility in organic solvents, which is due to their axial ligands on the central silicon. Maree *et al.* further indicate that silicon phthalocyanines substituted on the phthalocyanine ring have decreased singlet oxygen quantum yields compared to their unsubstituted silicon phthalocyanine counterparts. Thus, Maree *et al.* teach that substitution of the silicon phthalocyanine is crucial for good singlet oxygen quantum yields and that this substitution has to be on the central silicon atom as opposed to on the phthalocyanine ring.

The present invention provides a number of new substituted di(hydroxy/alkoxy)silicon phthalocyanines and their uses of in photodynamic therapy and in photodiagnostics. In a number of cases the biological activity of the new substituted di(hydroxy/alkoxy)silicon phthalocyanines is compared with that of similarly substituted zinc phthalocyanines.

Brief description of the invention

According to a first aspect of the present invention, there is provided a substituted di(hydroxy/alkoxy)silicon phthalocyanine of formula (I)



(I)

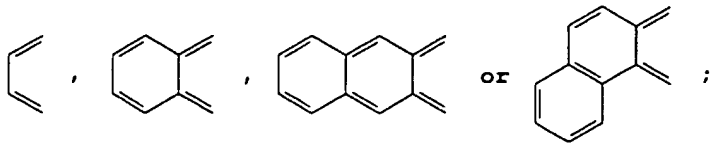
wherein m are the same or different and each m is 0, 1, 2, 3 or 4, provided that not all four m are simultaneously 0;

R^1 are the same or different and each R^1 is C_1-C_{20} alkyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$ and/or $-R^4-N-(R^5)_2$; C_2-C_{20} alkenyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$ and/or $-R^4-N-(R^5)_2$; C_2-C_{20} alkynyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-R^4-N-(R^5)_2$, $-Si(R^5)_3$, $-C_5H_4N$, $-C_4H_3S$ and/or $-C_6H_5$; $-R^4-O-R^5$; $-R^4-S-R^5$; $-R^4-SO_3H$; $-R^4-SO_2R^5$; $-R^4-SO_2N(R^5)_2$; $-R^4-N-(R^5)_2$; $-R^4-P-(R^5)_2$; $-R^4-P(O)(OR^5)_2$; $-R^4$–aryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-OR^5$, $-SO_3H$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$; $-R^4$–heteroaryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$; $-R^4-COR^5$; $-R^4-COOR^5$; $-R^4-CON(R^5)_2$; –F; –Cl; –Br; –I or $-B(OH)_2$; where

$-R^4$– are the same or different and each $-R^4$– is a chemical bond, $-(CH_2)_q$– with q being an integer from 1 to 20, or $-(CH_2)_aCH=CH(CH_2)_b$– with a and b being integers from 0 to 20 and the sum of a and b being from 0 to 20; and

$-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl optionally substituted, hetereoaryl optionally substituted or H, or two $-R^5$ together form a saturated or unsaturated ring;

R^2 are the same or different and each R^2 is



;

X are the same or different and each X is –H, $-CH_3$ or $-CH_2CH_3$,

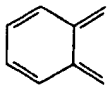
provided that not on all four substituent-units simultaneously have

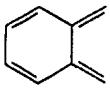
R^2 =  , one non-peripheral $R^1 = -(SCH_2CH_2)_3$-$N(CH_2CH_3)_2$, one non-peripheral R^1 = –Cl, and both peripheral $R^1 = -O$-C_6H_4-p-Cl, or

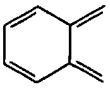
R^2 =  , one non-peripheral $R^1 = -O^iC_5H_{11}$, one non-peripheral $R^1 = -O^iC_4H_9$, and both peripheral $R^1 = -CH_3$, or

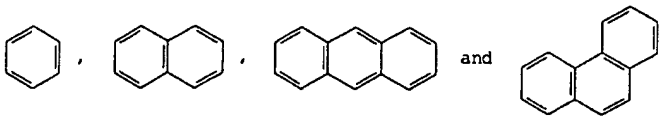
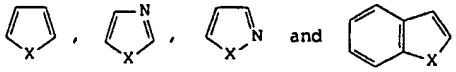
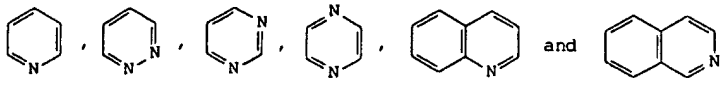
R^2 =  , both non-peripheral $R^1 = -O^nC_5H_{11}$ or $-OC_8H_{17}$, and both peripheral $R^1 = -SC_6H_5$, or

R^2 =  , and all four $R^1 = -CH_2C_6H_5$, or

R^2 =  or  , both non-peripheral $R^1 = -O^nC_4H_9$, and all two or four peripheral $R^1 = -H$,

R^2 =  , one peripheral $R^1 = -Cl$ or $-Br$, and all five remaining $R^1 = -H$, or

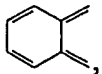
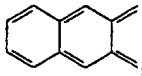
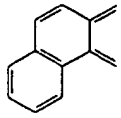
R^2 =  , both peripheral $R^1 = -OC_6H_5$, and both non-peripheral $R^1 = H$.

For the purpose of the present invention, "alkyl" is defined as a hydrocarbon with an sp^3 hybridised α-carbon, which may be straight chain or branched, and which may optionally be substituted, and which may comprise at least one double bond and/or at least one triple bond. "Aryl" is defined as an aromatic hydrocarbon with an sp^2 hybridised aromatic α-carbon, which may optionally be substituted. Examples of aryls are  . "Heteroaryl" is defined as an aromatic hydrocarbon with an sp^2 hybridised aromatic α-carbon, which comprises at least one heteroatom N, O or S as part of the aromatic ringsystem, and which may optionally be substituted. Examples of heteroaryls are  , where X = NH, O or S,  . "Alkenyl" is defined as a hydrocarbon with an sp^2 hybridised α-carbon, which may be branched or unbranched, and which may optionally be substituted. Examples of alkenyl groups are $-CH=CH_2$,

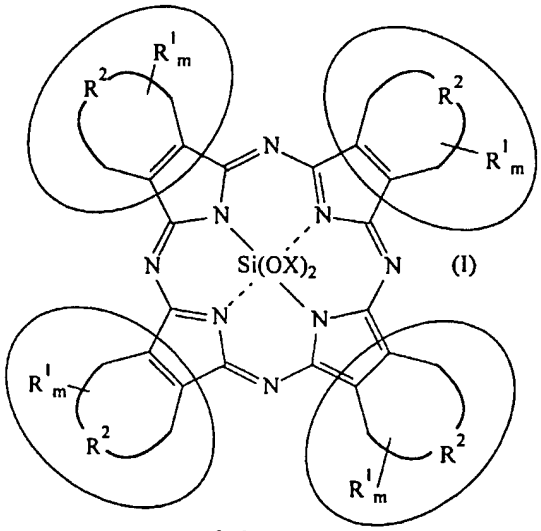
$-CH=CH-CH_3$, $-CH=CH-C_6H_5$, $-CH=CH-CH=CH_2$ and $-CH=CH-CH_2-CH=CH_2$. "Alkynyl" is defined as a hydrocarbon with an sp hybridised α-carbon, which may be branched or unbranched, and which may optionally be substituted. Examples of alkynyl groups are $-C\equiv C-H$, $-C\equiv C-CH_3$, $-C\equiv C-C_6H_5$ and $-C\equiv C-C\equiv C-H$. "Terminally alkenyl" and "terminally alkynyl" refers to terminal "alkenyl" and "alkynyl" groups respectively.

For the purpose of the present invention, an optionally substituted alkyl group may be substituted with one or more of –F, –Cl, –Br, –I, –OH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$ and/or $-R^4-N-(R^5)_2$. An optionally substituted alkenyl group may be substituted with one or more of –F, –Cl, –Br, –I, –OH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$ and/or $-R^4-N-(R^5)_2$. An optionally substituted alkynyl group may be substituted with –F, –Cl, –Br, –I, –OH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-R^4-N-(R^5)_2$, $-Si(R^5)_3$, $-C_5H_4N$, $-C_4H_3S$ and/or $-C_6H_5$. An optionally substituted aryl group may be substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, $-CH_2OH$, –F, –Cl, –Br, –OH, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$. An optionally substituted heteroaryl group may be substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$. In all of the above optional substitution patterns, $-R^4-$ are the same or different and each $-R^4-$ is a chemical bond, $-(CH_2)_q-$ with q being an integer from 1 to 20, or $-(CH_2)_aCH=CH(CH_2)_b-$ with a and b being integers from 0 to 20 and the sum of a and b being from 0 to 20; and $-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl optionally substituted, hetereoaryl optionally substituted or H, or two $-R^5$ together form a saturated or unsaturated ring.

For the purpose of the present invention, a "non-peripheral" substituent is defined as a substituent α to the point of fusion between the pyrrole ring and the R^2 containing aromatic ring in a compound of formula (I), (IA), (IB) or (V), or α to either one of the two cyano groups in a compound of formula (II), (III), (IV), (VI) or (VII). A substituent is defined as "peripheral" when it is not "non-peripheral". For example, in Scheme 1 above, the non-peripheral substituents are in positions 1, 4, 8, 11, 15, 18, 22 and 25 and the peripheral substituents are in positions 2, 3, 9, 10, 16, 17, 23 and 24.

When R^2 is  , then the compounds of formula (II), (III), (IV), (VI) and (VII) of the present invention are substituted benzenes. When R^2 is  , then the compounds of formula (II), (III), (IV), (VI) and (VII) of the present invention are substituted naphthalenes. When R^2 is  , then the compounds of formula (II), (III), (IV), (VI) and (VII) of the present invention are substituted anthracenes. When R^2 is  , then the compounds of formula (II), (III), (IV), (VI) and (VII) of the present invention are substituted phenanthrenes.

A substituted phthalocyanine is made up of a core structure and four substituent-units X. The four substituent-units X are shown encircled in Scheme 2 below. As will be appreciated, depending on the substituents R^1, a substituted phthalocyanine can be mixed or non-mixed. A non-mixed phthalocyanine is a phthalocyanine made up of four identical substituent-units X. A mixed phthalocyanine is a phthalocyanine made up of at least two different substituent-units, preferably a mixed phthalocyanine is made up of two different substituent-units X^1 and X^2, wherein the ratio of X^1:X^2 may be 1:3, 2:2 or 3:1. When the ratio of X^1:X^2 is 2:2, the pairs of identical substituent-units X^1 or X^2 may be adjacent to each other or opposite each other.



Scheme 2

The substituted phthalocyanine of the present invention may be a non-mixed or a mixed phthalocyanine.

Preferably R^1 are the same or different and each R^1 is C_1-C_{20} alkyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$ and/or $-N(R^5)_3^+$; C_2-C_{20} alkenyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$ and/or $-N(R^5)_3^+$; C_2-C_{20} alkynyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-Si(R^5)_3$, $-C_5H_4N$, $-C_4H_3S$ and/or $-C_6H_5$; $-OR^5$; $-SR^5$; $-SO_2R^5$; $-N-(R^5)_2$; $-P-(R^5)_2$; $-P(O)(OR^5)_2$; –aryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-OR^5$, $-SO_3H$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$; –heteroaryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$; $-COR^5$; $-COOR^5$; $-CON(R^5)_2$; –F; –Cl; –Br; –I or $-B(OH)_2$; where $-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl, heteroaryl or H, or two $-R^5$ together form a saturated or unsaturated ring.

More preferably R^1 are the same or different and each R^1 is C_1-C_{20} alkyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$ and/or $-NHR^5$; C_2-C_{20} alkenyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$ and/or $-NHR^5$; C_2-C_{20} alkynyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$ and/or $-NHR^5$; $-OR^5$; $-SR^5$; $-SO_2R^5$; $-N-(R^5)_2$; $-P-(R^5)_2$; –aryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-OR^5$, $-SO_3H$, $-NH_2$ and/or $-NHR^5$; –heteroaryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-NH_2$ and/or $-NHR^5$; $-COR^5$; $-COOR^5$; $-CON(R^5)_2$; –F; –Cl; –Br or –I; where $-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl, hetereoaryl or H, or two $-R^5$ together form a saturated or unsaturated ring.

Alternatively, preferably R^1 are the same or different and each R^1 is C_1-C_{20} alkyl substituted with at least one or more of –F, –Cl, –Br, –I, –OH, $-NH_2$, $-NHR^5$, $-N(R^5)_2$

and/or $-N(R^5)_3^+$; C_2-C_{20} alkenyl; C_2-C_{20} alkynyl; $-S-R^5$; $-N-(R^5)_2$; -aryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, -F, -Cl, -Br, -OH, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$; -F; -Cl; -Br or -I; where $-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl, heteroaryl or H, or two $-R^5$ together form a saturated or unsaturated ring.

More preferably R^1 are the same or different and each R^1 is C_1-C_{20} alkyl fully substituted with -F, -Cl and/or -Br; C_2-C_{20} alkenyl; C_2-C_{20} alkynyl; $-S-R^5$; -aryl, optionally substituted with one or more of $-CH_3$, $-NO_2$, $-OCH_3$, -F, -Cl, -Br, -OH and/or $-NH_2$; -F; -Cl; -Br or -I; where $-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl, heteroaryl or H, or two $-R^5$ together form a saturated or unsaturated ring.

Preferably at least one R^1 is a non-peripheral substituent.

Most preferably R^1 are the same or different and are attached to the phthalocyanine ring by a carbon atom. In particular, most preferably R^1 are the same or different and each R^1 is C_1-C_{20} alkyl, optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, $-OR^5$, and/or $-SR^5$; C_2-C_{20} alkenyl, optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, $-OR^5$, and/or $-SR^5$; C_2-C_{20} alkynyl, optionally substituted with one or more of -F, -Cl, -Br, -I, -OH, $-OR^5$, and/or $-SR^5$; -aryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, -F, -Cl, -Br, -OH, $-OR^5$, and/or $-SR^5$; where $-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl, heteroaryl or H, or two $-R^5$ together form a saturated or unsaturated ring. Even more preferably R^1 are the same or different and each R^1 is C_1-C_{20} alkyl. Most preferably R^1 are the same or different and each R^1 is C_1-C_{10} alkyl.

X is either -H, or X is selected from -Me or -Et. Preferably X is -H.

Optionally the substituted phthalocyanine of formula (I) is substituted with or conjugated to an amino acid, a fatty acid, a nucleic acid, a di-, tri- or up to decapeptide, a

polypeptide, a protein, a saccharide, a polysaccharide or a polymer, preferably the substituted phthalocyanine of formula (I) is substituted or conjugated via R^1.

Preferably R^2 is  .

Preferably m is 1 or 2.

Preferably, $R^1_{n1} = R^1_{n2} = -C_5H_{11}$ or $-C_6H_{13}$, $R^1_{p1} = R^1_{p2} = -H$, and $R^2 =$  .

Optionally the substituted phthalocyanine forms a sandwich complex.

Optionally the substituted phthalocyanine forms a multimer. Preferably the multimer comprises at least two phthalocyanines. More preferably the at least two phthalocyanines forming the multimer are covalently linked, most preferably via R^1.

Optionally the substituted phthalocyanine is conjugated to a carrier, or entrapped or embedded in a carrier. Preferably the carrier is an amino acid, a fatty acid, a nucleic acid, a di-, tri- or up to decapeptide, a polypeptide, a protein, a saccharide, a polysaccharide or a polymer, most preferably conjugated via R^1. When the carrier is a polypeptide, the polypeptide is preferably an antibody.

When the carrier is a polymer, the substituted phthalocyanine is preferably entrapped or embedded in a solid polymer, or preferably conjugated to a soluble polymer. Preferably the solid polymer is selected from polyesters, poly(orthoesters), polyanhydrides, tyrosine derived pseudo-poly(amino acids) or polyphosphazenes, or wherein the soluble polymer is selected from N-(2-hydroxypropyl)methacrylamide (HMPA) copolymers, polyvinylpyrrolidone (PVP), poly(ethylene glycol) (PEG) polymers, copolymers or block copolymers, amino acid derived polymers or polyesters. Preferably the solid or soluble polymer is a biodegradable polymer.

Preferably the substituted phthalocyanine of the present invention is for use as a medicament. Preferably the medicament is for use in photodynamic therapy. Alternatively the medicament is for use in photodiagnostics.

According to a second aspect of the present invention, there is provided a pharmaceutical composition comprising a substituted phthalocyanine according to the present invention or a pharmaceutically acceptable salt thereof in a mixture or in association with a pharmaceutically acceptable carrier, diluent or excipient.

Preferably the pharmaceutical composition is in a form suitable for topical, subcutaneous, mucosal, parenteral, systemic, intra-articular, intra-venous, intra-muscular, intra-cranial, rectal or oral application.

Preferably the pharmaceutical composition of the present invention is for use in the photodynamic therapy of a human or animal disease. Preferably the human or animal disease is characterised by benign or malignant cellular hyperproliferation or by areas of neovascularisation. Preferably the human or animal disease is a viral, fungal or bacterial disease or a disease caused by prions. Preferably the human or animal disease is a tumour, rheumatoid arthritis, inflammatory arthritis, hemophilia, osteoarthritis, vascular stenosis, vascular restenosis, atheromas, hyperplasia, intimal hyperplasia, benign prostate hyperplasia, psoriasis, mycosis fungoides, eczema, actinic keratosis or lichen planus.

Alternatively the pharmaceutical composition of the present invention may be for use in photodiagnostics.

Alternatively the pharmaceutical composition of the present invention may be for use in the inactivation of a microorganism. Preferably the microorganism comprises Gram positive bacteria, Gram negative bacteria, yeasts, fungi, algae or parasites at any stage in their development.

According to a third aspect of the present invention, there is provided a composition comprising a substituted phthalocyanine according to the present invention for use in the inactivation of a microorganism. Preferably the microorganism comprises Gram

positive bacteria, Gram negative bacteria, yeasts, fungi, algae or parasites at any stage in their development.

Preferably the source of illumination for use with the pharmaceutical or non-pharmaceutical composition of the present invention is a laser or a non-coherent light source emitting light of optimal wavelength.

According to a fourth aspect of the present invention, there is provided a use of a substituted phthalocyanine of the present invention for the manufacture of a phototherapeutic agent for the use in photodynamic therapy. Preferably the phototherapeutic agent is used for the treatment of a disease characterised by benign or malignant cellular hyperproliferation. Preferably the phototherapeutic agent is used for the treatment of a viral, fungal or bacterial disease or a disease caused by prions. Preferably the phototherapeutic agent is used for the treatment of a disease such as a tumour, rheumatoid arthritis, inflammatory arthritis, hemophilia, osteoarthritis, vascular stenosis, vascular restenosis, atheromas, hyperplasia, intimal hyperplasia, benign prostate hyperplasia, psoriasis, mycosis fungoides, eczema, actinic keratosis and lichen planus.

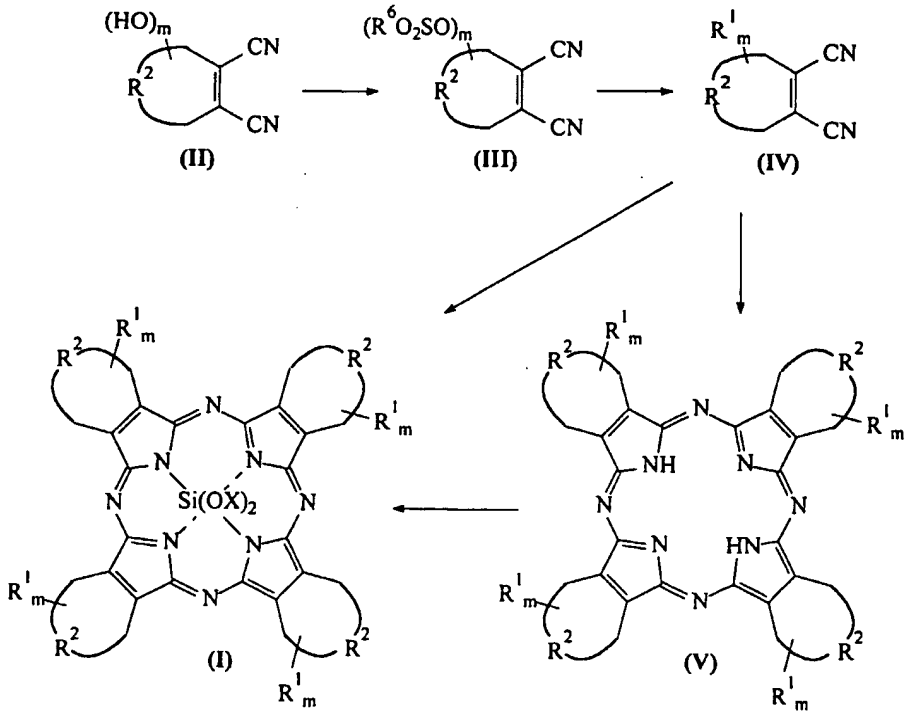
According to a fifth aspect of the present invention, there is provided a use of a substituted phthalocyanine of the present invention for the manufacture of a photodiagnostic agent for the identification of areas that are pathologically affected by cellular hyperproliferation.

According to a sixth aspect of the present invention, there is provided a material comprising a substituted phthalocyanine of the present invention, wherein the optical or physical properties of the material may be altered by incident radiation. Preferably the incident radiation is electromagnetic radiation. More preferably the incident radiation is electromagnetic radiation with a wavelength in the range of from 200nm to 1000nm.

Detailed description of the invention

As can be seen in Scheme 3, a substituted di(hydroxy/alkoxy)silicon phthalocyanine (I) may be prepared either by the cyclisation of a substituted phthalonitrile

(IV) either by itself or together with any other phthalonitrile of formula (IV), or by the metallation of a metal-free phthalocyanine (V). Alternatively, a substituted di(hydroxy/alkoxy)silicon phthalocyanine (I) may be prepared by trans-metallation of a metallated phthalocyanine such as for example a lithium phthalocyanine (not shown). A metal-free phthalocyanine (V) may be prepared either by the cyclisation of a substituted phthalonitrile (IV) either by itself or together with any other phthalonitrile of formula (IV), or by the de-metallation of a metallated phthalocyanine (not shown), for example a magnesium phthalocyanine. A phthalonitrile of formula (IV) may be prepared from a phthalonitrile sulfonate ester (III), which in turn may be prepared from a suitable phthalonitrile alcohol (II).



Scheme 3

A phthalonitrile sulfonate ester of formula (III) may be prepared from a phthalonitrile alcohol of formula (II) under suitable conditions. The preparation of 3,6-(trifluoromethanesulfonyloxy) phthalonitrile (a triflate), 2,3-dicyano-1,4-(trifluoromethanesulfonyloxy)naphthalene (a triflate) and 3,6-(nonafluorobutanesulfonyloxy)phthalonitrile (a nonaflate) are now described as

representative examples of the preparation of phthalonitrile sulfonate esters of formula (III).

Aryl triflates (trifluoromethanesulfonyls) are usually prepared from phenols in excellent yields by treating them with triflic anhydride in the presence of a base such as triethylamine or pyridine at low temperature (K. Ritter, *Synthesis*, 1993, page 735; P.J. Stang, M. Hanack, L.R. Subramanian, *Synthesis*, 1982, page 82). However, the reaction of 2,3-dicyanohydroquinone with either triethylamine or pyridine and triflic anhydride at -20°C was ineffective due to the low solubility of the starting material in both solvents. Addition of a co-solvent such as CH_2Cl_2 was also ineffective. However, the hydroquinone could be triflated in high yield (91%) by using either 2,6-lutidine or 2,4,6-collodine as the base in the presence of CH_2Cl_2. Thus, to a solution of dicyanohydroquinone in a 3:1 CH_2Cl_2/lutidine mixture at -20°C was added triflic anhydride dropwise under argon. After stirring for one day at room temperature, a simple aqueous work-up followed by recrystallisation from CH_2Cl_2/petrol or EtOAc/cyclohexane afforded 3,6-(trifluoromethanesulfonyloxy)phthalonitrile as yellow crystals in good yield. 2,3-Dicyano-1,4-(trifluoromethanesulfonyloxy)naphthalene was prepared by a similar procedure.

Aryl nonaflates (nonafluorobutanesulfonyls) are usually prepared from phenols by treatment with nonafluorobutanesulfonyl fluoride. However, attempts to nonaflate the 2,3-dicyanohydroquinone under the above conditions all met with failure, possibly due to the poorer leaving group ability of the fluoride anion compared with the triflate anion. However, using sodium hydride as the base in THF led to a clean and high yielding reaction to afford after a simple aqueous work-up 3,6-(nonafluorobutanesulfonyloxy)-phthalonitrile.

A substituted phthalonitrile of formula (IV) may be prepared from a sulfonate ester of formula (III) under various conditions, such as for example cross-coupling with an organozinc reagent or an organocopper reagent catalysed by palladium (Method A) or nickel (Method B), cross-coupling with a trialkylborane catalysed by palladium (Method C), cross-coupling with a boronic acid or ester catalysed by palladium (Method D), S_NAr reaction with a nucleophiles (Method E), or coupling with a suitable coupling partner catalysed by palladium (Method F). These methods shall now be described in turn.

Methods A and B – Cross-coupling between a phthalonitrile sulfonate ester of formula (III) and an organozinc reagent or an organocopper reagent catalysed by palladium or nickel to yield an alkyl-substituted phthalonitrile of formula (IV):

The cross-coupling reaction between an aryl iodide and an organozinc reagent catalysed by palladium (Negishi reaction) was first reported in 1977 by Negishi and co-workers (E. Negishi, A.O. King, N. Okukado, *J. Org. Chem.*, 1977, vol. 42, page 1821). The reaction was somewhat overlooked until renewed interest in the late 80's (P. Knochel, J.J.A. Perea, P. Jones, *Tetrahedron*, 1998, vol. 54, page 8275). Unlike organolithiums or Grignard reagents, which also undergo cross-coupling reactions, organozincs are unreactive to a wide range of functional groups (P. Knochel, R.D. Singer, *Chem. Rev.*, 1993, vol. 93, page 2117). This is important since it allows a range of functional groups to be incorporated in the reaction, either on the organozinc reagent itself, or on the coupling partner. Functional groups which can be tolerated include ketones, esters, amides, nitriles, acetals, alkenes and alkynes. Besides aryl and alkenyl halides, aryl and alkenyl triflates can also be used as coupling partners (K. Ritter, *Synthesis*, 1993, page 735; P. Knochel, J.J.A. Perea, P. Jones, *Tetrahedron*, 1998, vol. 54, page 8275; E. Erdik, *Tetrahedron*, 1992, vol. 48, page 9577).

Polyfunctional organozinc halides are readily prepared by direct insertion of zinc into alkyl iodides. Thus decylzinc iodide was prepared by adding a concentrated solution (*ca.* 3M) of 1-iododecane in THF to a suspension of zinc dust (3 equivalent) in THF at 40°C. The zinc dust was activated with a few mol% of dibromoethane and TMSCl prior to the addition of the halide. After 12 hours at 40°C the preparation of decylzinc iodide was complete.

Several alternatives also exist. The organozincs can be prepared by metathesis of a Grignard or organolithium reagent with anhydrous $ZnBr_2$ or $ZnCl_2$ in THF. This method was also applied for the generation of decylzinc chloride. However a number of problems exist with this route, firstly the $MgCl_2$ by-product tends to clog the stirrer and makes transfer by cannula problematic and secondly the $ZnCl_2$ is very hygroscopic and therefore

difficult to dry. However, 1-octynylzinc chloride was successfully prepared by metathesis of 1-octynyllithium with $ZnCl_2$ at –78°C.

The third method of note is the insertion of more activated zinc (Rieke zinc), prepared by the reduction of zinc halides, into less active alkyl bromides or even aryl bromides. Thus treatment of $ZnCl_2$ with finely cut lithium in the presence of naphthalene produces highly reactive zinc which reacts, for example with methyl 3-bromobutyrate in refluxing THF to afford the secondary zinc reagent (L. Zhu, R.M. Wehmeyer, R.D. Rieke, *J. Org. Chem.*, 1991, vol. 56, page 1445; M.V. Hanson, R.D. Rieke, *J. Am. Chem. Soc.*, 1995, vol. 117, page 10775; M.V. Hanson, R.D. Rieke, *Tetrahedron*, 1997, vol. 53, page 1925).

Many aryl and heteroarylzinc halides are available by using one of the three methods above (P. Knochel, J.J.A. Perea, P. Jones, *Tetrahedron*, 1998, vol. 54, page 8275). The direct zinc insertion into iododecane is preferred for the preparation of the simple alkylzinc reagent decylzinc iodide. 1-Octynylzinc chloride was best prepared by metathesis of 1-octynyllithium and $ZnCl_2$ at –78°C. A more exotic zinc reagent 6-chlorohexylzinc bromide [$Cl(CH_2)_6ZnBr$] was purchased from the Aldrich chemical company. This was prepared by insertion of Rieke zinc. Rieke zinc as a solution in THF can also be purchased from Aldrich.

Initially the cross-coupling reaction was attempted under the more usual conditions of palladium catalysis (method A). Various palladium catalysts have been used for the reaction including $Pd(PPh_3)_4$ (E. Erdik, *Tetrahedron*, 1992, vol. 48, page 9577), bis(tri-*o*-tolylphosphine)palladium(II) dichloride (E. Nakamura, I. Kuwajima, *Tetrahedron Lett.*, 1986, vol. 27, page 83), $PdCl_2$(dppf) (T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.*, 1984, vol. 106, page 158) and bis(tri-*o*-furylphosphine)palladium(II) dichloride (V. Farina, B. Krishnan, *J. Am. Chem. Soc.*, 1991, vol. 113, page 9585). The latter three catalysts bearing loosely bound bulky phosphine ligands help to prevent the formation of biaryls by phenyl transfer from triphenylphosphine and give excellent results.

The $Pd(PPh_3)_4$ catalysed cross-coupling of 3,6-(trifluoromethanesulfonyloxy)-phthalonitrile with decylzinc iodide is described as a representative example of cross-coupling reactions of method A. Lithium chloride was added as a co-catalyst. Although its exact role is not known, it helps to prevent biaryl formation and stabilises the catalyst (M. Fujita, H. Oka, K. Ogura, *Tetrahedron Lett.*, 1995, vol. 36, page 5247; K. Ritter, *Synthesis*, 1993, page 735).

Thus, to a solution of 3,6-(trifluoromethanesulfonyloxy)phthalonitrile, $Pd(PPh_3)_4$ (5 mol%) and LiCl (3 equivalent) in THF was added decylzinc iodide (2.5 equivalent) and the reaction refluxed under argon for 12 hours. After cooling and filtration to remove precipitated palladium, TLC analyses showed a mixture of 3,6-didecylphthalonitrile (by comparison with a known sample), and a slower running component, presumably 3-decyl-6-(trifluoromethanesulfonyloxy)-phthalonitrile. Thus, as expected, palladium has been shown to be a viable catalyst in cross-coupling reactions of method A.

Nickel catalysis (method B) is an attractive alternative to palladium catalysis, both in terms of the cost of the metal and the increased reactivity of Ni(0) towards oxidative insertion into a carbon-halogen or carbon-triflate bond. Snieckus and co-workers have examined the cross-coupling reaction of organotriflates with arylzinc reagents under a variety of conditions (C.A. Quesnell, O.B. Familoni, V. Snieckus, *Synlett*, 1994, page 349). They examined a number of nickel catalysts including $Ni(acac)_2$, $Ni(acac)_2/PPh_3$ and $NiCl_2(PPh_3)_2$. All catalysts were active to varying degrees, although PPh_3 stabilised Ni(0) catalysts were among the most reactive. More recently a report by Lipshutz and co-workers demonstrated the nickel catalysed cross-coupling of aryl chlorides and one aryl triflate with alkylzinc reagents using a $NiCl_2(PPh_3)_2/2PPh_3$ catalyst (B.H. Lipshutz, P.A. Blomgren, S-K. Kim, *Tetrahedron Lett.*, 1999, vol. 40, page 197).

The $NiCl_2(PPh_3)_2/2PPh_3$ catalysed cross-couplings of 3,6-(trifluoromethanesulfonyloxy)phthalonitrile with decylzinc iodide, 6-chlorohexylzinc bromide and 1-octynylzinc chloride are described as representative examples of cross-coupling reactions of method B.

The Ni(0) catalyst was generated *in situ* by the treatment of $NiCl_2(PPh_3)_2$ (10 mol%) and PPh_3 (20 mol%) in THF at room temperature with *n*-BuLi (20 mol%) to afford a blood-red Ni(0) catalyst [$Ni(PPh_3)_4$]. DIBAL or MeMgBr can be used instead of *n*-BuLi to generate the catalyst (C.A. Quesnell, O.B. Familoni, V. Snieckus, *Synlett*, 1994, page 349). To this catalyst was added 3,6-(trifluoromethanesulfonyloxy)phthalonitrile as a solid at room temperature under a stream of argon. The resulting solution was cooled to -78°C, and decylzinc iodide (2.5 equivalent) containing LiCl (2.5 equivalent) was added as a solution in THF. The reaction was allowed to warm to room temperature and stirred at that temperature for 16 hours. The reaction was then quenched with 5% HCl, and extracted with ethyl acetate. The organics were washed with further acid and base, dried and concentrated until precipitation began. The resulting solution was allowed to crystallise to afford 3,6-didecylphthalonitrile contaminated with PPh_3. The PPh_3 could be removed by stirring the solid in acetonitrile, in which 3,6-didecylphthalonitrile is insoluble. A further filtration afforded the product as white crystals in 60-70% yield.

By using 6-chlorohexylzinc bromide as the zinc reagent under identical conditions to those described above, 3,6-bis(6'-chlorohexyl)phthalonitrile was readily produced in 61% yield. The introduction of a halogenated alkyl chain is not readily performed by the thiophene and furan routes of the prior art described earlier. 3,6-Bis(4'-chlorobutyl)phthalonitrile, 3,6-bis(4-pivaloyloxybutyl)phthalonitrile, 3,6-bis(4-t-butyldimethylsilyloxybutyl)phthalonitrile, and 3,6-bis(1,1-H-2,2-H-perfluorodecyl)-phthalonitrile were prepared similarly. Of course, those practised in the art will recognize that functionality within the substituent chain can be changed by standard functional group interconversion chemistry. To exemplify this, 3,6-bis(6'-chlorohexyl)phthalonitrile was reacted with imidazole to form the 3,6-bis(6'-imidazol-1-yl-hexyl)phthalonitrile. Terminal hydroxy groups at the end of the substituents are readily accessible from some of the functionality described. Conversion of appropriately substituted phthalonitriles can be used to generate dimeric or oligomeric structures by standard reactions, for example terminal alcohol groups reacting with diesters or diacid chlorides.

The use of an alkynylzinc chloride reagent, prepared from an alkynyllithium reagent with $ZnCl_2$, led to the preparation of alkynyl-substituted phthalonitriles. Thus, 3,6-bis(1'-octynyl)phthalonitrile was prepared by the cross-coupling of 1-octynylzinc chloride.

In general the chemistry is readily performed, although the careful exclusion of water from the reaction is necessary. Lipshutz indicates that for the less reactive aryl chlorides the addition of the organozinc reagent is best performed at -78°C. An attempt to reproduce the coupling using decylmagnesium chloride rather than decylzinc iodide failed, with only polymeric products being formed. The much more reactive Grignard reagent is probably attacking the nitrile functionality.

Method C – Cross-coupling between a phthalonitrile sulfonate ester of formula (III) and a trialkylborane catalysed by palladium to yield an alkyl-substituted phthalonitrile of formula (IV):

The reaction of aryl halides and aryl triflates with boron reagents has been extensively investigated by Suzuki and co-workers (N. Miyaura, A. Suzuki, *Chem. Rev.*, 1995, vol. 95, page 2457). The cross-coupling of an aryl compound with an alkylboron reagent (Suzuki-Miyaura reaction) is a powerful tool for the formation of aryl-alkyl carbon bonds and has been investigated for both aryl halides (N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Sato, A. Suzuki, *J. Am. Chem. Soc.*, 1989, vol. 111, page 314) and aryl triflates (T. Oh-e, N. Miyaura, A. Suzuki, *J. Org. Chem*, 1993, vol. 53, page 2201).

Alkyl boron reagents are readily available from the hydroboration of alkenes, and thus a wide range of alkyl groups can theoretically be introduced. The most common alkyl transfer reagent used is a 9-alkyl-9-BBN derivative, whereupon the primary alkyl group is transferred preferentially. This is prepared from an alkene and 9-BBN. However the use of simple trialkylborons, prepared from alkenes and BH_3, is more economical due to the expense of 9-BBN.

The cross-coupling involves the treatment of an aryl triflate with a palladium catalyst, a boron reagent and a base at high temperature (50-90°C), typically in a solvent such as THF or 1,4-dioxane. The base is essential for the reaction to proceed, greatly increasing the nucleophilicity of the organoboron and accelerating the subsequent transmetalation step with the organopalladium complex (K. Matos, J.A. Soderquist, *J. Org. Chem.*, 1998, vol. 63, page 461). A variety of bases has been used for the reaction,

although some of the most successful such as NaOMe (A. Furstner, G. Seidel, *J. Org. Chem.*, 1997, vol. 62, page 2332) and NaOH (T. Oh-e, N. Miyaura, A. Suzuki, *J. Org. Chem*, 1993, vol. 53, page 2201) are clearly incompatible with the nitrile functionality. Thus, weaker bases, such as K_2CO_3 and K_3PO_4, were investigated (K. Matos, J.A. Soderquist, *J. Org. Chem.*, 1998, vol. 63, page 461). Again several palladium catalysts have been used for the reaction, the most successful being $PdCl_2$(dppf).

The results gained under a variety of conditions, all using tridecylborane, are summarised below, see Table 1. All reactions had LiCl (3 equivalent) added as a co-catalyst. The best results were obtained when tridecylborane was produced *in situ*, that is a solution of borane (0.33 equivalent) in THF was added to 1-decene at 0°C. After stirring for 4 hours the formation of the tridecylborane was complete and the base was added. After stirring for a further 1 hour to allow formation of the borate complex, palladium catalyst and 3,6-(trifluoromethanesulfonyloxy)phthalonitrile were added and the reaction refluxed for 10 hours. The solvents were removed under reduced pressure and the residue purified by column chromatography to afford 3,6-didecylphthalonitrile in moderate yields. The low yields obtained are perhaps due to the effect of the base on the phthalonitrile, as considerable black baseline material was also formed.

Catalyst	**Base**	**Solvent**	**Temperature**	**Yield**
$Pd(PPh_3)_4$	K_2CO_3	THF	Reflux (55)	No product
$Pd(PPh_3)_4$	K_3PO_4	THF	Reflux (55)	No product
$Pd(PPh_3)_4$	NaOH (aq)	THF	Reflux (55)	No product
$Pd(PPh_3)_4$	K_3PO_4	Dioxane	Reflux (85)	No product*
$PdCl_2$(dppf)	K_3PO_4	THF	Reflux (55)	38%*
$PdCl_2$(dppf)	K_2CO_3	THF	Reflux (55)	29%*

Table 1. (* indicates tridecylborane was formed *in situ*.)

Method D – Cross-coupling between a phthalonitrile sulfonate ester of formula (III) and a boronic acid or ester catalysed by palladium or nickel to yield a substituted phthalonitrile of formula (IV):

The cross-coupling of an aryl compound with a boronic acid or ester (Suzuki reaction) is a general method to couple an aromatic ring to an unsaturated coupling partner. The reaction involves the palladium or nickel catalysed coupling of a boronic acid or ester with an aryl halide or triflate under mild base catalysis. The mild conditions allow the inclusion of a wide-range of functionality on either coupling partner.

The $Pd(PPh_3)_4$ catalysed cross-couplings of 3,6-bis(trifluoromethanesulfonyloxy)-phthalonitrile with phenylboronic acid, 3-methoxyphenylboronic acid and 4-methoxyphenylboronic acid respectively are described as representative examples of cross-coupling reactions of method D. To a solution of 3,6-(trifluoromethanesulfonyloxy)-phthalonitrile in toluene was added LiCl (2.5 equivalent) and $Pd(PPh_3)_4$ (6 mol%) under argon. Phenylboronic acid was added, followed by aqueous Na_2CO_3 as a base, and the reaction was refluxed for 14 hours. A simple aqueous work-up followed by recrystallisation from toluene afforded 3,6-diphenylphthalonitrile in 79% yield. 3,6-Bis(4-methoxyphenyl)phthalonitrile and 3,6-bis(3-methoxyphenyl)phthalonitrile were prepared in a similar way by cross-coupling of 3,6-(trifluoromethanesulfonyloxy)phthalonitrile with 4-methoxyphenylboronic acid and 3-methoxyphenylboronic acid respectively.

Method E – S_NAr reaction of a phthalonitrile sulfonate ester of formula (III) with a nucleophile to yield a substituted phthalonitrile of formula (IV):

Nucleophilic aromatic substitution (S_NAr) reactions are unfavourable due to electronic and steric reasons. S_NAr reactions that nevertheless occur are thought to proceed either via a Meisenheimer complex or a benzyne intermediate. Arenes containing strongly electron-withdrawing groups ortho and/or para to the site of substitution may undergo S_NAr reactions via an addition / elimination process (Meisenheimer complex). Treating arenes with a strong base can induce S_NAr reactions via an elimination / addition process (benzyne intermediate).

The S_NAr reactions of 3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile with alkyl thiols from hexylthiol through to dodecylthiol are described as representative examples of reactions of method E. Typically, the reaction of 3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile in DMF with dodecanethiol and K_2CO_3

resulted in an S_NAr substitution of the triflate after stirring for 72 hours at room temperature. The reaction of 3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile with the other alkyl thiols under similar conditions also resulted in an S_NAr substitution of the triflate. These reactions represent a facile synthesis of the 3,6-bis(alkylsulfanyl)-phthalonitrile series.

Amino-substituted phthalonitriles may also be synthesised via method E, using amines such as for example piperidine, morpholine, pyrrolidine or piperazine as nucleophiles, and has been exemplified using the first one of these. S_NAr conditions could possibly be favoured by using Cs_2CO_3 as the base and the nonaflate rather than the triflate (see for example L. Neuville, A. Bigot, M.E.T.H. Dau, J. Zhu, *J. Org. Chem.*, 1999, vol. 64, page 7638). Alternatively palladium catalysed amination may be a viable route (A.J. Belfield, *Tetrahedron*, 1999, vol. 55, page 11399).

Method F – Coupling between a phthalonitrile sulfonate ester of formula (III) and an unsaturated coupling partner catalysed by palladium to yield a substituted phthalonitrile of formula (IV):

The coupling of an alkene and an aryl halide or triflate is known as the Heck reaction. Again the reaction is palladium catalysed and generally occurs at high temperature in the presence of an amine base.

The palladium catalysed coupling of 3,6-bis(trifluoromethanesulfonyloxy)-phthalonitrile with 1-decene is described as a representative example of coupling reactions of method F. The reaction was attempted using 3,6-bis(trifluoromethanesulfonyloxy)-phthalonitrile and 1-decene under typical conditions. Thus 3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile, 1-decene, $Pd(PPh_3)_4$ (6 mol%), LiCl and Et_3N were heated to 100°C in DMF for 24 hours. This resulted in extensive formation of baseline material, from which none of the expected product could be isolated. After testing different solvents (DMF, CH_3CN) and catalysts ($Pd(PPh_3)_4$, $PdCl_2(dppf)$, $Pd(OAc)_2/PPh_3$) without success, it was reasoned that the organic base (Et_3N) was interfering with the reaction, possibly by attack at the triflate. Repeating the reaction with the hindered base, 2,6-lutidine, led to the expected di-alkenylphthalonitrile being isolated. Yields may

possibly be improved by the use of different bases, both organic (for example DBU) and inorganic (for example Cs_2CO_3), and new catalysts (for example palladacycles, $Ni(PPh_3)_4$, etc.).

A metallated substituted phthalocyanine of formula (I) or a non-metallated substituted phthalocyanine of formula (V) may be prepared from a substituted phthalonitrile of formula (IV) under suitable conditions. 3,6-Bis(dodecylsulfanyl)phthalonitrile was successfully cyclised into both the metal-free and metallated phthalocyanines using $NH_3(g)$ in DMAE. The cyclisation to form metallated derivatives can also be brought about using DBU as base. This afforded magnesium phthalocyanines bearing eight decylsulfanyl groups through to hexylsulfanyl groups. Metal free analogues are available by acid catalysed hydrolysis of the magnesium derivatives, exemplified by the demetallation of the octakis(nonylsulfanyl)-phthalocyaninato magnesium(II) derivative. The Q-band of these phthalocyanines is significantly red-shifted, occurring between 780 and 830 nm.

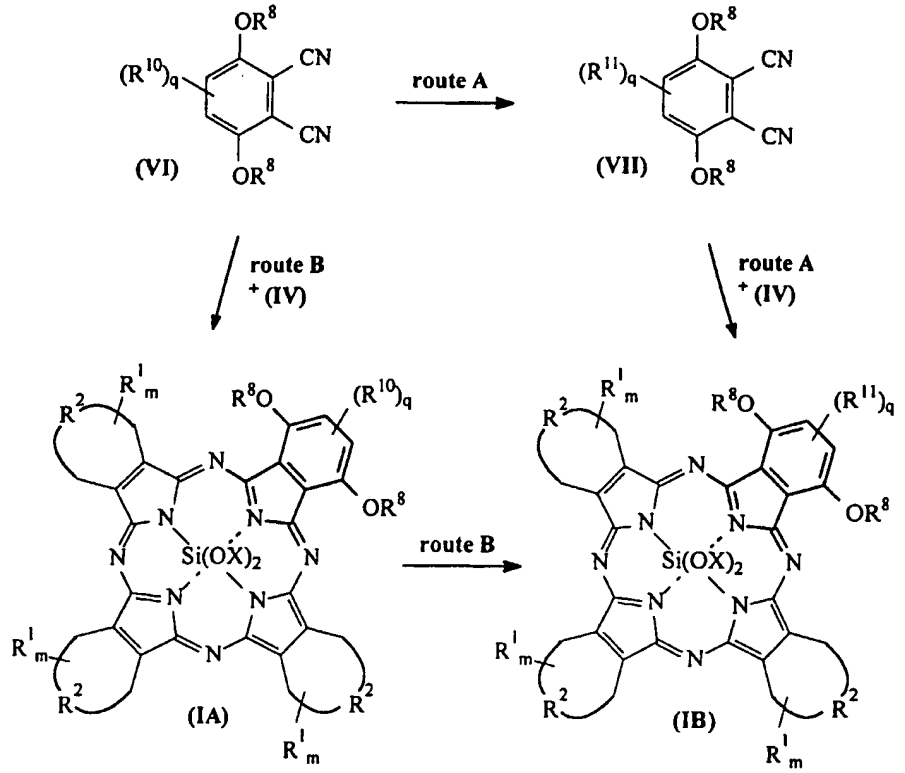
Other 3,6-bis(substituted)phthalonitrile precursors can be similarly cyclotetramerised to give the corresponding metallated or non-metallated phthalocyanines. For example, 3,6-bis(1,1-H-2,2-H-perfluorodecyl)phthalonitrile was converted into the corresponding octa(1,1-H-2,2-H-perfluorodecyl)phthalocyanine, soluble in fluorinated solvents.

Of course, 1:3 and 2:2 mixed substituted phthalocyanines may also be prepared making use of methods A to F described above, by cyclising a substituted phthalonitrile of formula (IV) together with any other substituted phthalonitrile (IV) instead of with itself. When it is desired to obtain a 1:3 mixed substituted phthalocyanine, the phthalonitrile giving rise to three substituent-units may be used in excess. By-products of the reaction include the non-mixed substituted phthalocyanine and the 2:2 mixed substituted phthalocyanines in which the pairs of common substituted isoindole units are either opposite or adjacent.

1:3 and 2:2 Phthalocyanines bearing functional groups on the pendant aromatic rings can provide access to further derivatives by standard chemistry. For example,

demethylation of the methoxy groups by reagents such as BBr_3 would lead to the corresponding phenolic derivatives. These could be used to link two or more phthalocyanine molecules together via diester linkages to form dimeric or oligomeric derivatives.

As can be seen in Scheme 4, a substituted di(hydroxy/alkoxy)silicon phthalocyanine (IA) or (IB) (the phthalocyanines (IA) and (IB) being a subgroup of phthalocyanines (I)) may also be prepared by the cyclisation of a substituted phthalonitrile (VI) or (VII) either by itself or together with any other phthalonitrile of formula (IV).



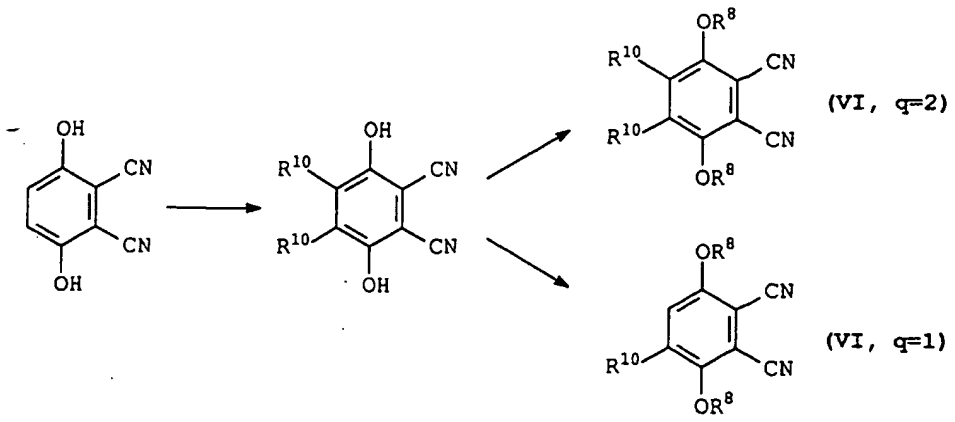
wherein R^8 are the same or different and each R^8 is C_1-C_{20} alkyl optionally substituted;

R^{10} are the same or different and each R^{10} is –Cl, –Br or –I;

R^{11} are the same or different and each R^{11} is –alkyl optionally substituted, –alkenyl optionally substituted, –alkynyl optionally substituted, –aryl optionally substituted or –heteroaryl optionally substituted.

Scheme 4

A substituted phthalonitrile of formula (VI) may in turn be prepared from 2,3-dicyanohydroquinone, as shown in Scheme 5.



Scheme 5

A phthalonitrile halide of formula (VI) may be prepared from 2,3-dicyanohydroquinone by halogenation and subsequent alkylation under suitable conditions.

For example, bromination of 2,3-dicyanohydroquinone affords 4,5-dibromo-3,6-dihydroxyphthalonitrile. The use of Guenther's method (T. Guenther, Justus Liebigs Ann. Chem., 1906, vol. 349, pages 56-58), bromine in acetic acid, provides a product which gives a low analysis for bromine. However, bromination of 2,3-dicyanohydroquinone using NBS (Roussel UCLFA, French Patent No. 1313082, 28th December 1962; *Chem. Abs.*, 1962, vol. 57, 11283h), followed by sodium metabisulfite reduction of the 2,3-dibromo-4,5-dicyanobenzoquinone so formed, gives 4,5-dibromo-3,6-dihydroxy-phthalonitrile in 66% yield.

Alkylation of 4,5-dibromo-3,6-dihydroxyphthalonitrile unexpectedly and fortuitously provides access to both 4,5-dibromo-3,6-dibutoxyphthalonitrile and 4-bromo-3,6-dibutoxyphthalonitrile. Thus iodobutane in the presence of potassium carbonate in MEK gives a mixture of 4,5-dibromo-3,6-dibutoxyphthalonitrile (6%) and 4-bromo-3,6-dibutoxyphthalonitrile (39%). The latter is formed exclusively (42%) by delaying addition of iodobutane to the basic solution. This implies that the role of the base is to eliminate HBr from 4,5-dibromo-3,6-dihydroxyphthalonitrile, presumably *via* its tautomer. The resulting mono-bromobenzoquinone may then be reduced back to the mono-bromohydroquinone, which then undergoes conventional Williamson's ether synthesis.

Conditions could not be found which favoured the formation of 4,5-dibromo-3,6-dibutoxyphthalonitrile over 4-bromo-3,6-dibutoxyphthalonitrile in this type of alkylation reaction. Instead, 4,5-dibromo-3,6-dibutoxyphthalonitrile is obtained conveniently and in satisfactory yield (84%) from 4,5-dibromo-3,6-dihydroxyphthalonitrile using Mitsunobu conditions.

A substituted di(hydroxy/alkoxy)silicon phthalocyanine of formula (IA) or (IB) may be prepared from a phthalonitrile halide of formula (VI) via two routes. Firstly (route A), the phthalonitrile halide (VI) may be converted into a substituted phthalonitrile (VII), which in turn is cyclised either by itself or together with any other phthalonitrile of formula (IV) to yield a substituted phthalocyanine of formula (IB). Alternatively (route B), the phthalonitrile halide (VI) may be cyclised either by itself or together with any other phthalonitrile of formula (IV) to yield a substituted phthalocyanine halide of formula (IA). The substituted phthalocyanine halide (IA) may optionally be converted into a substituted phthalocyanine of formula (IB).

Substituted phthalocyanines having one phthalonitrile-monomer different from the other three (1:3 mixed substituted phthalocyanines) may be synthesised, for example, by making use of solid-phase synthetic methods (*Tet. Letts.*, 1982, vol. 23(30), pages 3023-3026; *J. Org. Chem.*, 1991, vol. 56, pages 82-90). The use of polystyrene-based resins as solid-phase has been discussed (EP-A-0,906,758). Obviously, phthalocyanines having four identical phthalonitrile-monomers may also be synthesised via solid-phase synthesis. 1:3 and 2:2 mixed substituted phthalocyanines can in principle be prepared by several methods, for example cross cyclotetramerisation (G. de la Torre, P. Vazquez, F. Agullo-Lopez, T. Torres, *J. Chem. Mat.*, 1998, vol. 8, pages 1671-1683; J. Bakboord, M.J. Cook, E. Hamuryudan, *J. Porphyrins Phthalocyanines*, 2000, vol. 4, pages 510-517).

To demonstrate the utility of routes A and B described above, route B has been followed using cross cyclotetramerisation to yield 1:3 mixed substituted phthalocyanines. Two appropriately substituted phthalonitriles (VI) and (IV) are reacted together; the desired product is separated from the resulting mixture by chromatography. For example, the mixed cyclotetramerisation of 4-bromo-3,6-dibutoxyphthalonitrile and 3,6-didecylphthalonitrile was investigated in order to obtain metal-free 1,4-dibutoxy-2-bromo-

8,11,15,18,22,25-hexakis(decyl)phthalocyanine. Lithium butoxide in butanol was used as base at different temperatures and over different reaction times, with and without the addition of Pd(0) as $Pd(PPh_3)_4$ as a co-catalyst. Ratios of phthalonitriles of 4:1, 3:1 (3,6-didecylphthalonitrile in excess) and 1:1 were investigated. A 1:1 ratio of precursors in dry butanol /lithium butoxide heated under reflux for 20 hours afforded a mixture of octakis(decyl)phthalocyanine and the 1:3 product, 1,4-dibutoxy-2-bromo-8,11,15,18,22,25-hexakis(decyl)phthalocyanine (as the lithiated derivatives). Also present were 2:2 products and compounds in which butoxy groups have displaced bromo substituents as judged by mass spectrometry. Unexpectedly, the addition of $Pd(PPh_3)_4$ as co-catalyst enhanced yields of both the octakis(decyl)phthalocyanine and the 1:3 product, 1,4-dibutoxy-2-bromo-8,11,15,18,22,25-hexakis(decyl)phthalocyanine. Furthermore, the latter was found to be the major product. However, it was contaminated with up to ca. 15% of the palladium metallated derivative, 1,4-dibutoxy-2-bromo-8,11,15,18,22,25-hexakis(decyl)phthalocyaninato palladium(II). The pure metal-free compound, 1,4-dibutoxy-2-bromo-8,11,15,18,22,25-hexakis(decyl)phthalocyanine, is isolated by column chromatography. 1,4-Dibutoxy-2,3-dibromo-8,11,15,18,22,25-hexakis(decyl)-phthalocyanine may be prepared similarly.

The 1,4-dibutoxy-2,3-dibromo-8,11,15,18,22,25-hexakis(decyl)phthalocyanine and 1,4-dibutoxy-2-bromo-8,11,15,18,22,25-hexakis(decyl)phthalocyanine may be converted into their ethynylated derivatives using the Sonogashira coupling method (K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.*, 1975, vol. 16, pages 4467-4470; S. Thorand, N. Krause, *J. Org. Chem.*, 1999, vol. 63, pages 8551-8553) leading to the trimethylsilyl (TMS) protected ethynylated phthalocyanines, or the Stille procedure (D.E. Rudisill, J.K. Stille, *J. Org. Chem.*, 1989, vol. 54, pages 5856-5866) leading directly to the unprotected ethynylated phthalocyanines.

Route A was also followed. 4-Bromo-3,6-dibutoxyphthalonitrile and 4,5-dibromo-3,6-dibutoxyphthalonitrile were cross-coupled with boronic acids using a palladium catalyst (Suzuki reaction). For example, 4-bromo-3,6-dibutoxyphthalonitrile and $Pd(PPh_3)_4$ (10mol%) were stirred in DME under nitrogen for 10 minutes. 2-Thiopheneboronic acid was added, followed by a 2M aqueous solution of Na_2CO_3. The mixture was refluxed for 12 hours. After cooling, a simple work-up followed by

recrystallisation afforded 4-(2-thienyl)-3,6-dibutoxyphthalonitrile in 62% yield. 4-Pyridyl-3,6-dibutoxyphthalonitrile, 4-phenyl-3,6-dibutoxyphthalonitrile, 4,5-diphenyl-3,6-dibutoxyphthalonitrile, 4-(*p*-hydroxymethylphenyl)-3,6-dibutoxyphthalonitrile and 4-(*p*-N,N-dimethylaminophenyl)-3,6-dibutoxyphthalonitrile, 4-(*p*-aminophenyl)-3,6-dibutoxyphthalonitrile, 4-(*p*-methoxyphenyl)-3,6-dibutoxyphthalonitrile and 4-(*p*-carboxyphenyl)-3,6-dibutoxyphthalonitrile were prepared in a similar way. The functionalised phenyl rings in these 4-aryl-3,6-dibutoxyphthalonitriles provide access to further derivatives by functional group interchange. Thus mesylation of 4-(*p*-hydroxymethylphenyl)-3,6-dibutoxyphthalonitrile followed by reaction with tyrosine methyl ester in the presence of base affords the corresponding 4-*p*-benzyloxy-O-tyrosine methyl ester phthalonitrile.

The versatility of the Suzuki reaction on the 4-bromo- and 4,5-dibromo-3,6-dibutoxyphthalonitriles in principle provides access to other amino acid derivatives, for example with phenylalanine groups para coupled directly to the phthalonitrile core, preferably using NH_2 and CO_2H protected derivatives of phenylalanine boronic acid or its ester (see F. Firooznia, C. Gude, K. Chan and Y. Satoh, *Tetrahedron Letters*, 1998, vol. 39, 3985).

Application of the Heck reaction (coupling alkenes to aromatic rings) and the Negishi reaction to 4-bromo- and 4,5-dibromo-3,6-dibutoxyphthalonitriles as precursors provides further means of incorporating functional groups at the 4- and 4,5-positions of 3,6-dibutoxyphthalonitrile. Thus reactions of 4-bromo-3,6-dibutoxyphthalonitrile with 4-chlorobutylzinc bromide and with 4-ethoxy-4-oxobutylzinc bromide afford the corresponding functionalised phthalonitriles, which are again in principle precursors to other functionally substituted alkyl substituents or can be linked to form dimeric phthalonitriles.

1:3 Mixed substituted phthalocyanines are then obtained from the 4-substituted- and 4,5-disubstituted-3,6-dibutoxyphthalonitriles using cross cyclotetramerisation as described above for route B. In this way various 1,4-dibutoxy-2-substituted-8,11,15,18,22,25-hexakis(decyl)phthalocyanines and 1,4-dibutoxy-2,3-disubstituted-

8,11,15,18,22,25-hexakis(decyl)phthalocyanines were prepared. Of course, phthalonitriles of formula (VII) can be cyclotetramerised alone to form further phthalocyanines.

Thus the present invention provides a substituted di(hydroxy/alkoxy)silicon phthalocyanine of formula (I) (including substituted di(hydroxy/alkoxy)silicon phthalocyanine of formulas (IA) and (IB)).

The substituted di(hydroxy/alkoxy)silicon phthalocyanines of the present invention show a multitude of desirable properties and are thus useful for a wide variety of applications.

In particular, the substituted di(hydroxy/alkoxy)silicon phthalocyanines of the present invention show high photodynamic properties and a marked absorption in the red region of the visible spectrum. These compounds are thus useful both as such and in the form of conjugates with macromolecular carriers (such as for example polymers or antibodies) in the treatment of viral, fungal or bacterial diseases and diseases characterised by areas of neovascularisation or by benign or malignant cellular hyperproliferation, in particular diseases such as tumours, rheumatoid arthritis, inflammatory arthritis, hemophilia, osteoarthritis, vascular stenosis, vascular restenosis, atheromas, hyperplasia, intimal hyperplasia, benign prostate hyperplasia, psoriasis, mycosis fungoides, eczema, actinic keratosis or lichen planus. Moreover, in so far as they are fluorophores, they may be used as photodiagnostic agents for the identification of areas that are pathologically affected.

Once organic molecules containing the chromofluorophore macrocycle of the phthalocyanine are photo-activated by irradiation, they are capable of generating hyper-reactive derivatives of oxygen, above all singlet-oxygen or radicals, which are characterised by a high degree of cytotoxicity, and hence are potentially interesting for therapeutic applications, such as photodynamic therapy and/or diagnostic applications (E. Ben-Hur and I. Rosenthal, Int. J. Radiat. Biol., 1985, vol. 47, pages 145-147).

Photosensitization is a process in which a photochemical reaction is induced to occur by the presence of a substance (the photosensitizer), which absorbs the light but is

itself substantially unchanged at the end of the reaction, the absorbed light energy being passed on to the main reactants. For example when hydrogen is exposed to light of wavelength 253.6nm no absorption of the light takes place and the hydrogen remains completely unaffected. If mercury vapour is added to the hydrogen, the mercury atoms are excited. When such an excited mercury atom collides with a hydrogen molecule, it can transfer some of its energy to the hydrogen, and cause it to dissociate into atoms. The hydrogen has apparently been made sensitive to the light, which it does not absorb. In some cases the photosensitizer is broken down and a photo-product is formed which may also possess suitable photodynamic properties. Similarly, oxygen can be made sensitive to the electromagnetic radiation it may not normally absorb by the presence of phthalocyanines or other "complex" organic molecules; some of which may have metals or metal salts incorporated.

In the photodynamic therapy of tumours, the substituted phthalocyanines are administered to a tumour-bearing subject, where they are taken up by the tumour at least to a certain extent. Following administration to the patient, photodynamic therapy may be carried out in a conventional manner, using light sources and delivery systems that are known in the art (for example see Phys. Med. Biol., 1986, vol. 31(4), pages 327-360). Upon selective irradiation with an appropriate light source the tumour tissue is destroyed via the dye mediated photogeneration of species such as singlet oxygen or other cytotoxic species such as free radicals, for example hydroxy or superoxide.

Biological studies of substituted phthalocyanines in photodynamic therapy have been conducted with water soluble sulfonated metallo-phthalocyanines (I. Rosenthal, Photochem. Photobiol., 1991, vol. 53(6), pages 859-870). Phthalocyanines comprising hydroxyl, amine or quaternary ammonium substituents have been described for photosensitization of cancer cells (C.C. Leznoff et al., Photochemistry and Photobiology, 1989, vol. 49(3), pages 279-284; D. Wohrle et al., Photochemistry and Photobiology, 1990, vol. 51(3), pages 351-356; D. Wohrle D. et al., Dyes and Pigments, 1992, vol. 18, pages 91-102; H. Dummin, J. Photochem. Photobiol., 1997, vol. 37(3), pages 219-229). Experiments of cancer phototherapy with phthalocyanines on laboratory animals have also been reported (H. Barr et al., Br. J. Surg., 1990, vol. 77, pages 93-96; K. Schieweck et al., Proc. SPIE, 1994, vol. 2078, pages 107-118; C. Ometto et al., Br. J. Cancer, 1996, vol. 74,

pages 1891-1899; J. Rousseau et al., J. Photochem. Photobiol., B: Biol., 1990, vol. 6, pages 121-132). Minnoch et al. (J. Photochem. and Photobiol., 1996, vol. 32(3), pages 159-164) and Brown et al. (Photochem. and Photobiol., 1967, vol. 65(3)) have described the *in vitro* activity of four phthalocyanine derivatives both on micro-organisms and on cell lines.

There are various criteria, which have to be met at least to some extent, if a compound is to be successful as a photosensitizer for use in photodynamic therapy, including the following:

a) High quantum yield of reactive species, such as singlet-oxygen or radicals;
b) Relatively low toxicity to the subject;
c) Capacity of being activated by radiation of high wavelength (preferentially in the red or near infra-red region of the spectrum), which is able to penetrate more deeply into the tissues as compared to radiation of shorter wavelength;
d) Selective accumulation by the cells that are responsible for a given pathological condition and fast elimination from the tissues that are not affected by the pathological condition;
e) Possibility of being conjugated to macromolecular carriers, albeit maintaining the characteristics of photosensitization efficiency; and
f) Solubility in suitable solvents to facilitate administration to a patient and physiological uptake and transport within the patient's body.

Certain substituted phthalocyanines are induced to act as photosensitizers by incident electromagnetic radiation of a suitable wavelength. This includes all suitable wavelengths of the electromagnetic spectrum. Preferably the electromagnetic radiation is somewhere in the range of ultra-violet to infra-red, even more preferably it is in the range visible-red to infra-red. Red light shows greater tissue penetration than light of shorter wavelengths. Preferably a photosensitizer absorbs laser light of a suitable wavelength, but other light sources may also be used, such as a tungsten halogen lamp.

Metallated phthalocyanines have been found to have better photosensitizing activity compared to metal-free phthalocyanines when the metal is diamagnetic. Particularly zinc (II) phthalocyanines have been found to be useful in photodynamic therapy. Conversely a paramagnetic metal renders the phthalocyanine inactive (I.

Rosenthal, E. Ben-Hur, "Phthalocyanines in Photobiology" in "Phthalocyanines, Properties and Applications", eds., C.C. Leznoff and A.B.P. Lever, V.C.H. Publishers, 1989).

Hydrophilic substituents or the conjugation to hydrophilic carriers can accelerate the metabolism of the phthalocyanines, enabling a fast *in vivo* elimination of the chromophore, and thus preventing the onset of cutaneous phototoxicity.

Some substituted phthalocyanines show photodynamic activity even at low oxygen concentration, thus being useful for the specific treatment of anaerobic microorganisms or the treatment of tumour diseases known to be characterised by a hypoxic environment.

Substituted phthalocyanines may also be conjugated to carriers to improve their pharmacological characteristics. The carriers are normally chosen from the group consisting of amino acids, fatty acids, nucleic acids, di-, tri- or up to decapeptides, polypeptides, proteins, saccharides, polysaccharides, polymers and antibodies, which may be tailored to attach themselves to the tumour site. Antibodies may be prepared from cultured samples of the tumour. Examples include P.L.A.P. (Placental Alkaline Phosphatase), H.M.F.G. (Human Milk Fat Globulin), C.E.A. (Carcino Embryonic Antibody) and H.C.G. (Human Chorionic Gonadotrophin). The phthalocyanine-carrier bond may occur between carboxyl or amine groups or by exploiting other known functional and reactive groups.

Furthermore, the substituted phthalocyanines of the present invention may be polymerised. Polymerisation may take place across double bonds in unsaturated side chains or by ester or amide formation or any other suitable polymerisation technique, which will be apparent to those skilled in the art. Any polymerisation may be achieved with little or no effect on the phthalocyanine ring itself, as it possesses high stability.

Pharmaceutical compositions, comprising a substituted di(hydroxy/alkoxy)silicon phthalocyanine of the present invention, as such or in form of a conjugate with a carrier, or a pharmaceutically acceptable salt thereof, in a mixture or in association with a pharmaceutically acceptable carrier, diluent or excipient, may be formulated according to well-known principles and may desirably be in the form of unit dosages determined in

accordance with conventional pharmacological methods. The unit dosage forms may provide a daily dosage of active compound in a single dose or in a number of smaller doses. Dosage ranges may be established using conventional pharmacological methods and are expected to lie in the range of from 1 to 60 mg/kg of body weight. Other active compounds may be used in the compositions or administered separately, or supplemental therapy may be included in a course of treatment for a patient. The pharmaceutical compositions may desirably be in a form suitable for topical, subcutaneous, mucosal, parenteral, systemic, intra-articular, intra-venous, intra-muscular, intra-cranial, rectal or oral application. Suitable carriers and diluents are well known in the art and the compositions may include excipients and other components to provide easier or more effective administration.

Thus the present invention provides a substituted phthalocyanine of formula (I) optionally conjugated to a carrier for use as a medicament, particularly for use in photodynamic therapy or photodiagnostics. The present invention further provides a pharmaceutical composition comprising a phthalocyanine of formula (I) or a pharmaceutically acceptable salt thereof, particularly for use in photodynamic therapy or photodiagnostics. The present invention further provides use of a substituted phthalocyanine of formula (I) for the manufacture of a phototherapeutic or photodiagnostic agent.

The present invention further provides a material comprising a substituted phthalocyanine of formula (I), wherein the optical or physical properties of the material may be altered by incident electromagnetic radiation.

A. Synthetic Experimental Details

Preparation of phthalonitrile sulfonate esters (III):

Preparation of 3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile:

A 2-necked flask equipped with a thermometer and a pressure equalising addition funnel was flame dried under argon. 2,3-Dicyanohydroquinone (5.2 g, 0.0325 mol) was dissolved in a mixture of dry CH_2Cl_2 (30 ml) and dry 2,6-lutidine (16 ml), and the resulting

yellow solution was cooled to -20°C. A solution of trifluoromethanesulfonic anhydride (22.1 g, 0.078 mol) in dry CH_2Cl_2 (10 ml) was added dropwise over 30 minutes. The resulting solution was allowed to warm to room temperature and stirred for 14 hours. The CH_2Cl_2 was removed under reduced pressure and ethyl acetate (50 ml) was added. The resulting solution was washed with 5% HCl (2 x 20 ml), 5% NaOH (2 x 20 ml, to remove starting material and mono-triflated compound) and brine (20 ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was recrystallised from ethyl acetate/cyclohexane to afford *3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile* (12.71 g, 92%) as pale yellow crystals [m.p. 109-111°C. Found C, 28.46; H, 0.29; N, 6.50. $C_{10}H_2N_2O_6S_2F_6$ requires C, 28.31; H, 0.48; N, 6.60. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.87 (s, 2H) ppm. ^{13}C NMR (270 MHz, $CDCl_3$) δ 148.89 (ArC-O), 128.66 (ArC-H), 118.55 (q, J = 321 Hz, -CF_3), 112.88, 109.32 ppm. ν_{max} (KBr) 3116 (m), 2254 (m, CN), 1473 (s), 1440 (s), 1231 (s), 1132 (s) cm^{-1}. MS (70 eV, EI) 423.9 (5.81%, M)$^+$].

Preparation of 2,3-dicyano-1,4-bis(trifluoromethanesulfonyloxy)naphthalene:

In a similar procedure to above, 2,3-dicyano-1,4-dihydroxynaphthalene (1.99 g, 9.47 mmol) was dissolved in dry CH_2Cl_2 (25 ml) and dry 2,6-lutidine (10 ml), and the resulting brown solution cooled to –20°C. A solution of trifluoromethanesulfonic anhydride (5.89 g, 3.5 ml, 2.2 eq) in dry CH_2Cl_2 (5 ml) was added dropwise over 30 minutes. The reaction was allowed to warm to room temperature and stirred for 18 hours. Work-up as above afforded the crude product, which was recrystallised from methanol to afford *2,3-dicyano-1,4-bis(trifluoromethanesulfonyloxy)naphthalene* (2.65 g, 59%) as pale yellow crystals [mp 114-115°C. Found: C, 35.58; H, 0.74; N, 5.82. $C_{14}H_4N_2O_6S_2F_6$ requires C, 35.45; H, 0.85; N, 5.90%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.38 (2H, dd), 8.12 (2H, dd) ppm. ^{13}C NMR (270 MHz, $CDCl_3$) δ 147.22 (ArC-O), 133.62 (ArC-H), 129.54, 123.85 (ArC-H), 118.46 (CF_3, q, J= 321 Hz), 110.39, 106.04 ppm].

Preparation of 3,6-bis(nonafluorobutanesulfonyloxy)phthalonitrile:

2,3-Dicyanohydroquinone (2.53 g, 0.0158 mmol) and 18-crown-6 (one crystal) were dissolved in dry THF (60 ml) and cooled to 0°C. Sodium hydride (60% dispersed in mineral oil, 1.45 g, 0.0363 mmol) was added portionwise. To the resulting yellow precipitate was added nonafluorobutanesulfonyl fluoride (10.85 g, 0.036 mmol) dropwise at 0°C. The reaction was allowed to warm to room temperature and stirred for 24 hours to

afford a pale green solution. The reaction was diluted with diethyl ether (50 ml), and washed with 5% NaOH (30 ml), 5% HCl (30 ml) and brine (30 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was recrystallised from CH_2Cl_2/CH_3OH (99:1) to afford *3,6-bis(nonafluorobutanesulfonyloxy)phthalonitrile* as white crystals [^1H NMR (300 MHz, acetone-d_6) δ 7.85 (s, 2H) ppm].

Preparation of phthalonitriles (IV) via methods A to F:

Preparation of Zinc dust (D.D. Perrin, W.L.F. Armarego, "Purification of Laboratory Chemicals", 3rd edition):

Zinc dust (120 g) was stirred in 2% HCl (300ml) for 2 minutes and the acid removed (decanter). The resulting dust was stirred sequentially with 2% HCl (300 ml), water (3 x 300 ml) and 95% ethanol (2 x 200ml), the dust being allowed to settle before the waste solvents were decantered. Finally the zinc was washed with diethyl ether (200 ml), filtered and dried under vacuum for 24 hours. The resulting dust was stored over P_2O_5.

Preparation of *n*-decylzinc iodide (see B. H. Lipshutz in "Organometallics in Synthesis. A Manual.", ed. M. Schlosser, John Wiley and Sons, 1994, Chichester):

To a flame-dried 2-necked flask, equipped with a reflux condensor and a rubber septum under argon, was added acid washed zinc dust (10 g, *ca.* 3 equivalent) and dry THF (3 ml). Dibromoethane (1.14 g, 6.07 mmol) in THF (2 ml) was added via syringe and the mixture was heated to ebullition with a hot air gun. The reaction was allowed to cool and then heated again. This process was repeated once more, then trimethylsilyl chloride (0.66 g, 6.07 mmol) was added. The mixture was again heated with a hot air gun and allowed to cool. The rubber septum was replaced by a pressure-equalising addition funnel charged with 1-iododecane (13.68 g, 51 mmol) in dry THF (25 ml), and the reaction heated to 40-45°C. The iododecane was added dropwise over 30 minutes, and then stirred for 12 hours at 40°C. The reaction was cooled and the excess zinc allowed to settle (4 hours). The resulting grey zinc reagent was transferred via a cannula to a dry storage vessel. The remaining zinc was washed with THF (10 ml), allowed to settle and transferred into the storage vessel to afford *n-decylzinc iodide* in THF (37 ml, at 1.24M assuming a 90% conversion). [NB. Complete reaction of iododecane can be checked by hydrolysing the zinc reagent and running a GC.]

Preparation of 3,6-didecylphthalonitrile: Method A

To a flame dried 2-necked flask under argon was added 3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile (1 g, 2.36 mmol), lithium chloride (0.30 g, 7.0 mmol), tetrakis(triphenylphosphine) palladium(0) (136 mg, 5 mol%) and dry THF (10 ml). After stirring for 10 minutes at room temperature, decylzinc iodide in THF (7.0 mmol, 20 ml of a 0.35M solution in THF) was added via a syringe and the resulting solution was stirred at room temperature for 30 minutes, and then refluxed for 12 hours. The solution was cooled, filtered and the solvent removed under reduced pressure. TLC (petrol/CH_2Cl_2 1:1) showed a mixture of 3,6-didecylphthalonitrile and a slower running fraction which was presumably 3-decyl-6-(trifluoromethanesulfonyloxy)phthalonitrile.

Preparation of 3,6-didecylphthalonitrile: Method B

To a flame-dried 2-necked flask was added bis(triphenylphosphine)-nickel (II) dichloride (0.154 g, 10 mol%) and triphenylphosphine (0.124 g, 20 mol%) under argon at room temperature. Dry THF (5 ml) was added followed by *n*-butyllithium (0.2 ml, 20 mol%, 2.5M in hexanes) to afford blood red slurry. 3,6-Bis(trifluoromethanesulfonyloxy)-phthalonitrile (1 g, 2.36 mmol) was added as a solid under a fast stream of argon, and the resulting pale brown solution was cooled to -78°C. Decylzinc iodide in THF (7.0mmol, 5.6ml of a 1.24M solution in THF) containing lithium chloride (0.30g, 7.0mmol) was added via a syringe and the resulting solution was warmed to room temperature over *ca.* 1 hour. The reaction was stirred at room temperature for 16 hours. 5% HCl (10ml) was carefully added, followed by ethyl acetate (20ml). The organic layer was separated, and washed with 5% HCl (10ml) and brine (10ml). The aqueous waste was back extracted with ethyl acetate (10ml), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was stirred in acetonitrile (10 ml) for 30 minutes and filtered to afford pure *3,6-didecylphthalonitrile* (0.67g, 70%), which was identical to a known sample.

Preparation of 3,6-dihexylphthalonitrile: Method B

The procedure for the synthesis of 3,6-didecylphthalonitrile was followed using 3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile (2 g, 4.73 mmol) and hexylzinc iodide in THF (10 ml, 14.19 mmol). The resulting oily crude product was purified using column

chromatography (silica gel, eluent: DCM/n-hexane 3:2) to afford *3,6-dihexylphthalonitrile* as a white solid (0.95 g, 68%) [Found: C, 81.07; H, 9.42; N, 9.31%. $C_{20}H_{28}N_2$ requires: C, 81.03; H, 9.52; N, 9.45%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 2H), 2.85 (t, 4H, J 7.7), 1.66 (quintet, 4H, J 7.5), 1.28-1.42 (m, 12H), 0.89 (t, 6H, J 7.0) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 133.5, 115.6, 115.2, 34.3, 31.3, 306, 28.7, 22.4, 13.9 ppm].

Preparation of 3,6-bis(4'-chlorobutyl)phthalonitrile: Method B

A mixture of triphenylphosphine (625mg, 2.4mmol), lithium chloride (1.5g, 35mmol) and bis(triphenylphosphine)nickel (II) chloride (780mg, 1.2mmol) was stirred in dry THF (25ml) under nitrogen for 10 minutes. *n*-BuLi (2.5M in hexanes, 1ml) was added to the blue solution at room temperature. The solution turned deep red. Solid 3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile (5g, 12mmol) was added at once under a fast stream of nitrogen and the pale brown solution was cooled to -78°C. 4-Chlorobutylzinc bromide (0.5M in THF purchased from Aldrich, 50ml, 25mmol) was added via a syringe. The solution was allowed to warm to room temperature and stirring continued for 12 hours under nitrogen. 5% HCl (50ml) was added and the mixture extracted with ethyl acetate (3x20ml). The combined organic layers were washed with 5% HCl (10ml), 5% NaOH (10ml), brine (10ml), and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica [eluent: petroleum ether (bp. 40-60°C) / dichloromethane, 1:1] to remove triphenylphosphine. The eluent was changed to dichloromethane to obtain *3,6-bis(4'-chlorobutyl)phthalonitrile* (1.92g, 6.2mmol, 52%) as a pale yellow oil which solidifies on standing [mp 61°C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.6 (s, 2H), 3.6 (t, 4H), 2.9 (t, 4H), 1.77 (m, 8H) ppm. m/z 308 (M, 21.47%), 310 (M+2, 15.42%)].

Preparation of 3,6-bis(6'-chlorohexyl)phthalonitrile: Method B

In a similar procedure to above, 3,6-bis(trifluoromethanesulfonyloxy)-phthalonitrile (0.5 g, 1.18 mmol) was added to the nickel catalyst [prepared from $NiCl_2(PPh_3)_2$ (78 mg) and PPh_3 (62.5 mg)]. The reaction was cooled to -78°C and 6-chlorohexylzinc bromide (0.5M in THF purchased from Aldrich, 5.5 ml, 2.75 mmol) was added via a syringe. The reaction was allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with 5% HCl and worked-up as above. The resulting crude product was

purified by column chromatography over silica (eluent: petrol/CH_2Cl_2 1:1) to afford triphenylphosphine as the first fraction, and *3,6-bis(6'-chlorohexyl)phthalonitrile* (0.26 g, 60.5%) as the second fraction [m.p. 44.5-45.5°C. Found: C, 66.07; H, 7.17; N, 7.67. $C_{20}H_{26}N_2Cl_2$ requires C, 65.75; H, 7.17; N, 7.67. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 2H), 3.54 (t, 4H, $-OCH_2$), 2.87 (t, 4H, $-CH_2Cl$), 1.83-1.63 (m, 8H), 1.53-1.26 (m, 8H) ppm].

Preparation of 3,6-bis[6'-(imidazol-1-yl)hexyl]phthalonitrile: (from the above compound)

A mixture of 3,6-bis(6'-chlorohexyl)phthalonitrile (720mg, 1.97mmol), imidazole (270mg, 4mmol), potassium carbonate (10 eq.) and tetra-*n*-butyl ammonium iodide (catalytic amount) in DMF (10ml) was heated at 60°C under nitrogen with stirring for 72 hours. After cooling, water (100ml) was added. A pale brown oil formed at the bottom of the flask and this was separated. Dichloromethane was added to the oil and the organic layer washed with water (2x20ml), brine (20ml) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent removed under reduced pressure. The product was separated (silica gel, eluent: dichloromethane, followed by methanol). The methanol fraction was evaporated to yield *3,6-bis[6'-(imidazol-1-yl)hexyl]phthalonitrile* (550mg, 1.3mmol, 66%) as a thick pale yellow oil [^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.62 (s, 2H), 7.59 (br s, 2H), 7.2 (br s, 4H), 4.2 (t, 4H), 2.91 (t, 4H), 1.86 (m, 4H), 1.75 (m, 4H), 1.4 (m, 8H) ppm. m/z 446 ($M+H_2O$)].

Preparation of 3,6-bis(4'-ethoxy-4'-oxobutyl)phthalonitrile: Method B

A mixture of triphenylphosphine (375mg, 1.4mmol), lithium chloride (0.9g, 21mmol) and bis(triphenylphosphine)nickel (II) chloride (470mg, 0.72mmol) was stirred in dry THF (15ml) under nitrogen for 10 minutes. *n*-BuLi (2.5M in hexanes, 0.6ml) was added to the blue solution at room temperature. The solution turned deep red. Solid 3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile (3g, 7.1mmol) was added at once under a fast stream of nitrogen and the pale brown solution was cooled to -78°C. 4-Ethoxy-4-oxobutylzinc bromide (0.5M in THF purchased from Aldrich, 30ml, 15mmol) was added via a syringe. The solution was allowed to warm to room temperature and stirring continued for 12 hours under nitrogen. 5% HCl (50ml) was added and the mixture extracted with ethyl acetate (3x20ml). The combined organics were washed with 5% HCl (10ml), 5% NaOH (10ml), brine (10ml), and dried ($MgSO_4$). The drying agent was

removed by filtration and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica (eluent: dichloromethane) to remove triphenylphosphine. The eluent was changed to ethylacetate to obtain *3,6-bis(4'-ethoxy-4'-oxobutyl)phthalonitrile* (1.6g, 4.5mmol, 63%) as a pale yellow oil which solidifies on standing [mp 51°C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.6 (s, 2H), 4.15 (q, 4H), 2.95 (t, 4H), 2.4 (t, 4H), 2.04 (m, 4H), 1.25 (t, 6H) ppm. m/z 311 (M-OEt, 5.59%)].

Preparation of 3,6-bis(4'-pivaloylbutyl)phthalonitrile: Method B

(a) 4-iodo-1-(pivaloyl)butane

To a stirred solution of dry THF (23.3g, 0.32mol) and pivaloyl chloride (12.06g, 0.1mol) in dry acetonitrile (200ml) was added sodium iodide (30g, 0.2mol). The flask was protected by a drying tube and stirred for 12 hours at room temperature. The resulting orange solution was quenched with sat. sodium metabisulfite (200ml). The mixture was extracted with diethyl ether (3x80 ml). The combined organics were washed with 5% NaOH (80ml), sat. sodium bisulfite (80ml), brine (80ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude oil was filtered through silica (eluent: diethyl ether/petrol 1:2). The first fraction afforded pure 4-iodo-1-(pivaloyl)butane (22.81g, 80.3%) [^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (t, 2H, J = 6.3 Hz), 3.22 (t, 2H, J = 6.8 Hz), 1.96-1.86 (m, 2H), 1.80-1.71 (m, 2H), 1.21 (s, 9H) ppm. IR (neat) 1729 (s, CO)]. The organozinc reagent from this compound was formed according to the procedure outlined above.

(b) coupling reaction

To a flame dried 3-necked flask under argon was added bis(triphenylphosphine)-nickel (II) dichloride (0.63g, 10mol%) and triphenylphosphine (0.50g, 20mol%). Dry THF (20ml) was added, followed by *n*-BuLi (2.5M in hexanes, 0.8ml, 20mol%) to afford a blood red slurry. 3,6-(Trifluoromethanesulfonyloxy)phthalonitrile (4g, 9.43mmol) and anhydrous LiCl (ca. 1.2g) were added together as solids under a fast stream of argon. The resulting pale brown solution was cooled to -78°C and 4-pivaloylbutylzinc iodide (0.024mol, 20ml of a 1.2M solution in THF) was added via a syringe. The solution was warmed to room temperature over *ca.* 1 hour, and the reaction stirred for 12 hours. Ethyl acetate (100ml) was added, and the solution washed twice with 5% HCl (40ml), brine (40ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. This was further purified by column chromatography over silica (eluent DCM). The first fraction contained

PPh_3. Subsequent fractions contained the product contaminated with triphenylphosphine and baseline material. A second column over silica (eluent: petrol/EtOAc 85:15 to 100:30) afforded *3,6-bis(4'-pivaloylbutyl)phthalonitrile* (2.57 g, 62%) as the second fraction as a colourless oil [Found: C, 70.87; H, 8.21; N, 6.28. $C_{26}H_{36}N_2O_4$ requires C, 70.88; H, 8.24; N, 6.36. IR (neat) 2958, 2871, 2229 (CN), 1727 (ester). ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 2H), 4.10 (t, 4H, J = 7.7 Hz), 2.91 (t, 4H, J = 7.2Hz), 1.78-1.61 (m, 8H), 1.20 (s, 18H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 178.63, 145.71, 133.48, 115.89, 114.86, 63.43, 38.58, 38.03, 33.80, 26.07, 27.00 ppm. MS (70 eV, EI) 440.1 (2.7%, M^+)].

Preparation of 3,6-bis(4'-*tert*-butyldimethylsilyloxybutyl)phthalonitrile: Method B

4-Iodo-1-(*tert*-butyldimethylsilyloxy)butane (*Synthesis* 1999, 1231; *Synthesis* 1998, 56) was converted into the zinc derivative and used according to the reaction above to afford 3,6-*bis(4'-tert-butyldimethylsilyloxybutyl)phthalonitrile* (27.6%) as a colourless oil [IR (neat) 2229 (CN). ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.13, 133.351, 115.83, 115.13, 62.49, 33.99, 32.01, 26.86, 25.84, 18.20, -5.48 ppm. ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 2H), 3.61 (t, 4H), 2.86 (t, 4H), 1.78-1.67 (m, 4H), 1.60-1.52 (m, 4H), 0.86 (s, 9H), 0.02 (s, 6H) ppm].

Preparation of 3,6-bis(1,1-H-2,2-H-perfluorodecyl)phthalonitrile: Method B

Prepared as above from 1,1-H-2,2-H-perfluorodecyl zinc iodide. After stirring at room temperature for 16 hours, the residue was dissolved in 250ml ether/THF (4:1) and washed with 5% HCl (40ml). An insoluble precipitate was formed and was filtered. The organic layer was washed with brine (40ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was stirred in acetonitrile (20ml) and filtered. The two filtrates were combined and recrystallised from α,α,α-trifluorotoluene to afford *3,6-bis(1,1-H-2,2-H-perfluorodecyl)phthalonitrile* (1.56g, 58%) [Found: C, 33.01; H, 0.82; N, 2.93. $C_{28}H_{10}N_2F_{34}$ requires C, 32.96; H, 1.06; N, 2.75. IR (smear) 2229 (CN). ^1H NMR (300 MHz, C_6F_6 containing 10% C_6D_6) δ 7.36 (s, 2H), 3.16 (t, 7.9 Hz), 2.57-2.41 (m, 4H) ppm].

Preparation of 3,6-bis(1'-octynyl)phthalonitrile: Method B

In a dry 2-necked flask under argon was added 1-octyne (2.20 g, 0.02 mol) and dry THF (10 ml). The reaction was cooled to –78°C and n-BuLi (2.5M solution in hexane, 8

ml, 0.02 mol) was added dropwise. The reaction was stirred for 30 minutes at –78°C. To the resulting yellow solution was added a solution of $ZnCl_2$ in Et_2O (1M, 20 ml, ALDRICH) over 10 minutes. The resulting white suspension was stirred at –78°C for 1 hour. Meanwhile, in another dry 2-necked flask the nickel catalyst was prepared. Thus, bis(triphenyl)phosphine-nickel(II) dichloride (0.53 g, 0.0008 mol) and triphenylphosphine (0.42 g, 0.0016 mol) were dissolved in dry THF (20 ml). n-BuLi (0.65 ml of a 2.5M solution in hexane, 0.0016 mol) was added dropwise to afford the active red catalyst. 3,6-(Trifluoromethanesulfonyloxy)phthalonitrile (3.40 g, 0.008 mol) was added as a solid under a fast stream of argon, the flask was cooled to –78°C, and the prepared solution of 1-octynylzinc chloride was added via a cannula. The reaction was allowed to warm to room temperature over ca. 1 hour and stirred at room temperature for 24 hours. The reaction was concentrated under reduced pressure and dissolved in ethyl acetate (100 ml). The ethyl acetate was washed with 5% HCl (2 x 20 ml), 5% NaOH (2 x 20 ml) and brine (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was further purified by column chromatography over silica (eluent: CH_2Cl_2/petrol 1:2 to 1:10). The first fraction afforded triphenylphosphine, whilst the second fraction contained *3,6-bis(1'-octynyl)phthalonitrile* (1.31 g, 48%) as a pale yellow oil which crystallised upon standing [^{1}H NMR (60 MHz, $CDCl_3$) δ 7.60 (s, 2H), 2.3 (t, 4H), 1.7-1.2 (m, 16H), 0.9 (t, 6H) ppm].

Preparation of 3,6-didecylphthalonitrile: Method C

To a flame dried 2-necked flask under argon was added 1-decene (0.51 g, 3.64 mmol) and dry THF (5 ml). The solution was cooled to 0°C and BH_3 in THF (1.2 mmol, 1.2 ml of a 1M solution in THF) was added dropwise. The reaction was stirred for 4 hours at 0°C. Dry THF (4 ml) and anhydrous potassium phosphate (0.85 g, 4 mmol) were added and the reaction stirred for 1 hour at room temperature. Anhydrous lithium chloride (0.08 g, 1.9 mmol) and 3,6-bis(trifluoromethanesulfonyloxy)phthalonitrile (0.25 g, 0.59 mmol) were added, followed after 10 minutes by $Pd(dppf)Cl_2$ [(1,1'-bis(diphenylphosphino) ferrocene)dichloropalladium (II)] (21 mg, 5 mol%). The reaction was heated at reflux for 10 hours. The reaction was cooled and filtered to remove palladium salts. The filtrate was concentrated under reduced pressure. The crude black product was further purified by column chromatography over silica (eluent: toluene) to afford *3,6-didecylphthalonitrile* (0.09 g, 38%).

Preparation of 3,6-diphenylphthalonitrile: Method D

3,6-Bis(trifluoromethanesulfonyloxy)phthalonitrile (0.5 g, 1.18 mmol) and anhydrous lithium chloride (0.13 g, 3 mmol) were stirred under argon in dry toluene (15 ml) for 30 minutes. Tetrakis(triphenylphosphine) palladium(0) (84.0 mg) was added and the mixture stirred for 10 minutes. Finally phenylboronic acid (0.43 g, mmol) was added followed by aqueous 2M Na_2CO_3 (2 ml). The reaction was heated under reflux for 14 hours, cooled and diluted with ethyl acetate (15 ml). The reaction was washed with 10% KOH (2 x 10 ml), 5% HCl (10 ml) and brine (10 ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was recrystallised from toluene to afford *3,6-diphenylphthalonitrile* (0.26 g, 79%) [m.p. 221-223.5°C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.63-7.51 (m, 10H) ppm].

Preparation of 3,6-bis(4-methoxyphenyl)phthalonitrile: Method D

3,6-Bis(trifluoromethanesulfonyloxy)phthalonitrile (0.5g, 1.18mmol) and anhydrous lithium chloride (0.13g, 3mmol) were stirred under argon in dry toluene (15ml) for 30 minutes. Tetrakis(triphenylphosphine)palladium(0) (84mg, 10mol%) was added and the mixture stirred for 10 minutes. Finally, 4-methoxyphenylboronic acid (0.45g, 3.5mmol, 2.5eq.) was added, followed by aqueous 2M Cs_2CO_3 (2ml). The reaction was heated under reflux for 14 hours, cooled and diluted with ethylacetate (15ml). The organics were washed with aqueous solutions of 10% KOH (2x10ml), 5% HCl (10ml), brine (10ml) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent was removed under reduced pressure. The crude product was recrystallised from toluene to afford *3,6-bis(4-methoxyphenyl)phthalonitrile* as white needles, 0.29g (0.86mmol, 73%). [mp. 213-215°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 2H), 7.55 (d, 4H, J= 8.5Hz), 7.06 (d, 4H, J= 8.6Hz), 3.89 (s, 6H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.07, 145.29, 134.0, 130.32, 128.91, 116.22, 115.49, 114.77, 55.56 ($\underline{C}H_3$) ppm. Found: C, 77.38; H, 4.68; N, 8.21%. $C_{22}H_{16}N_2O_2$ requires: C, 77.63; H, 4.74; N, 8.23%. m/z (EI) 340 (21%), 262 (100%). ν_{max} (nujol) 2224 (CN) cm^{-1}].

Preparation of 3,6-bis(3-methoxyphenyl)phthalonitrile: Method D

3,6-Bis(trifluoromethanesulfonyloxy)phthalonitrile (0.5g, 1.18mmol) and anhydrous lithium chloride (0.13g, 3mmol) were stirred under argon in dry toluene (15ml)

for 30 minutes. Tetrakis(triphenylphosphine)palladium(0) (84mg, 10mol%) was added and the mixture stirred for 10 minutes. Finally, 3-methoxyphenylboronic acid (0.45g, 3.5mmol, 2.5eq.) was added, followed by aqueous 2M Cs_2CO_3 (2ml). The reaction was heated under reflux for 14 hours, cooled and diluted with ethylacetate (15ml). The organics were washed with aqueous solutions of 10% KOH (2x10ml), 5% HCl (10ml), brine (10ml) and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent was removed under reduced pressure. The crude product was recrystallised from toluene to afford *3,6-bis(3-methoxyphenyl)phthalonitrile* (0.28g, 0.82mmol, 70%) as white crystals [mp. 236-239°C. ^{13}C NMR (300 MHz, $CDCl_3$) δ 160.22, 145.97, 137.84, 134.12, 130.45, 121.26, 115.96, 115.78, 115.55, 114.57, 55.59 ppm. Found C, 77.54; H, 4.64; N, 8.24. $C_{22}H_{16}N_2O_2$ requires C, 77.63; H, 4.74; N, 8.23%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.45 (t, 2H, J= 8Hz), 7.16 (ddd, 2H, J= 1, 0.8, 4.9 and 1Hz), 7.11 (t, 2H, J= 2.5 and 1.6Hz), 7.06 (ddd, 2H, J= 1, 0.8, 4.9, and 1Hz), 3.89 (s, 6H) ppm. m/z (EI) 340 (100%). ν_{max} (nujol) 2224 (CN) cm^{-1}].

Preparation of 3,6-bis(dodecylsulfanyl)phthalonitrile: Method E

3,6-Bis(trifluoromethanesulfonyloxy)phthalonitrile (2.00 g, 4.71 mmol) and dodecanethiol (4.51 g, 22.4 mmol) were stirred in dry DMF (20 ml) under nitrogen. Anhydrous potassium carbonate (5 g, excess) was added in portions over 4 hours, and the reaction stirred at room temperature for 72 hours. The reaction was poured into cold water (100 ml) and filtered. The filtrate was washed with water (50 ml) and methanol (50 ml). The mother liquor and washings were combined and extracted with ethyl acetate (2 x 100 ml). The combined organics were washed with 5% NaOH (50 ml) and brine (50 ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting yellow solid was combined with the original filtrate and recrystallised from CH_2Cl_2/ethyl acetate. The resulting yellow needles were filtered and washed with petrol (to remove dodecanethiol traces) to afford *3,6-bis(dodecylsulfanyl)phthalonitrile* (1.74 g, 70%) [m.p. 97.8-101.2°C. ^1H NMR (270 MHz, $CDCl_3$) δ 7.49 (s, 2H), 3.01 (t, 4H), 1.70-1.20 (m, 40H), 0.88 (t, 6H) ppm].

Preparation of 3,6-bis(decylsulfanyl)phthalonitrile: Method E

In a typical procedure, finely crushed potassium carbonate (2.3g, excess) and decanethiol (3.30g, 19.0mmol) were stirred in dry DMF (10ml) under nitrogen. 3,6-

Bis(trifluoromethanesulfonyloxy)phthalonitrile (2.00g, 4.7mmol) was added in portions over 2 hours, and the reaction stirred at room temperature for 72 hours. The reaction was poured into cold 5% NaOH (150ml), and filtered. The mother liquor was extracted with ethyl acetate (3x50ml). The combined organic solutions were washed with 5% NaOH (50ml), 5% HCl (50ml), brine (50ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting yellow solid was combined with the original filtrate and recrystallised from DCM/ethyl acetate. The resulting yellow needles were washed with petrol and dried to afford *3,6-bis(decylsulfanyl)phthalonitrile* (68%) [Found: C, 71.31; H, 9.38; N, 5.85. $C_{28}H_{44}N_2S_2$ requires: C, 71.14; N, 9.39; N, 5.93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 2H), 3.02 (t, 4H, J = 7.5 Hz), 1.68 (quint, 4H, 7.4 Hz), 1.47-1.25 (m, 28H), 0.88 (t, 6H, J = 6.7 Hz) ppm].

The following were prepared similarly:

3,6-Bis(dodecylsulfanyl)phthalonitrile [yield: 70%. Found: C, 71.94; N, 9.74; N, 5.03. $C_{32}H_{52}N_2S_2$ requires C, 72.67; N, 9.91; N, 5.30. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.49 (s, 2H), 3.01 (t, 4H, J = 7.4 Hz), 1.72-1.64 (m, 4H), 1.50-1.24 (m, 36H), 0.88 (t, 6H, J = 6.4 Hz) ppm].

3,6-Bis(undecylsulfanyl)phthalonitrile [yield: 63%. mp 92-93°C. Found: C, 71.53; H, 9.62; N, 5.40. $C_{30}H_{48}N_2S_2$ requires: C, 71.94; H, 9.66; H, 5.59. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 2H), 3.02 (t, 4H, J = 7.2 Hz), 1.72-1.64 (m, 4H), 1.50-1.25 (m, 32H), 0.88 (t, 6H, J = 6.7 Hz) ppm].

3,6-Bis(nonylsulfanyl)phthalonitrile [yield: 65%. mp 86-88°C. Found: C, 70.11; H, 8.91; N, 6.10. $C_{26}H_{40}N_2S_2$ requires: C, 70.22; H, 9.07; N, 6.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 2H), 3.02 (t, 4H, J = 7.4 Hz), 1.73-1.63 (m, 4H), 1.52-1.25 (m, 24H), 0.89 (t, 6H, J = 6.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.60, 132.30, 117.37, 114.06, 33.91, 31.88, 29.44, 29.25, 29.20, 28.74, 22.70, 14.12 ppm].

3,6-Bis(octylsulfanyl)phthalonitrile [yield: 27%. mp 91-92°C. Found: C, 69.20; H, 8.74; N, 6.56. $C_{24}H_{36}N_2S_2$ requires: C, 69.19; H 8.72; N, 6.73%. ^{1}H NMR (300 MHz, $CDCl_3$) δ

7.50 (s, 2H), 3.03 (t, 4H, J = 7.4 Hz), 1.69 (quint, 4H, 7.4 Hz), 1.45 (quint, 4H), 1.28 (m, 16H), 0.89 (t, 6H, J = 6.7 Hz) ppm].

3,6-Bis(heptylsulfanyl)phthalonitrile [yield: 46%. Found: C, 67.50; H, 8.21; N, 7.07. $C_{22}H_{32}N_2S_2$ requires: C, 68.01; H 8.31; N, 7.21%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 2H), 3.03 (t, 4H, J = 7.5 Hz), 1.70 (quint, 4H, 7.4 Hz), 1.46 (m, 4H), 1.31 (m, 12H), 0.91 (t, 6H, J = 6.7 Hz) ppm].

3,6-Bis(hexylsulfanyl)phthalonitrile [yield: 53%. mp 82-83.5°C. Found: C, 66.60; H, 7.81; N, 7.72. $C_{20}H_{28}N_2S_2$ requires: C, 66.62; H, 7.83; N, 7.77. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 2H), 3.03 (t, 4H, J = 7.4 Hz), 1.73-1.63 (m, 4H), 1.50-1.24 (m, 12H), 0.90 (t, 6H, J = 6.9 Hz) ppm].

Preparation of 1,4-bis(decylsulfanyl)-2,3-naphthalonitrile: Method E

1,4-Bis(trifluoromethanesulfonyloxy)-2,3-naphthalonitrile (0.5g, 1.05 mmol) and decanethiol (3eq, 0.56g, 3.15mmol) were stirred in dry DMF (5ml) under nitrogen. Anhydrous caesium carbonate (1.14g, excess) was added in portions over 4 hours and the reaction stirred at room temperature for 72 hours. The reaction mixture was poured into cold water (25ml) and the mixture filtered. The solid was washed with water (25ml). The mother liquor and washings were combined and extracted with EtOAc (2x25ml). The combined extracts were washed with aqueous NaOH 5% (25ml), brine (25ml), dried (Na_2SO_4), and evaporated to dryness. The resulting yellow solid was combined with the earlier filtrate. Recrystallisation from acetone afforded *1,4-bis(decylsulfanyl)-2,3-naphthalonitrile* (0.30g, 46%) [mp 76°C. Found: C, 73.35; H, 8.83; N, 5.24. $C_{32}H_{46}N_2S_2$ requires: C, 73.51; H 8.86; N, 5.35%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.81 (m, 2H), 7.87 (m 2H), 3.07 (t, 4H, J = 7.3 Hz), 1.6-1.2 (m, 32H), 0.87 (t, 6H, J = 6.85) ppm].

Preparation of 3,6-bis-piperidinylphthalonitrile: Method E

Dry piperidine (distilled over CaH_2) (3ml) was stirred under argon. 3,6-Bis(trifluoromethanesulfonyloxy)phthalonitrile (0.5g, 1.18mmol) was added and the reaction stirred for 72 hours. The flask was placed in the fridge and *3,6-bis-piperidinylphthalonitrile* precipitated as yellow crystals. These were filtered and washed

with acetonitrile (160mg, 0.54mmol, 46%) [^{1}H NMR (270 MHz, DMSO-d_6) δ 6.77 (s, 2H), 2.8 (br s, 8H), 1.5 (br s, 12H) ppm].

Preparation of 3,6-bis(1'-decenyl)phthalonitrile: Method F

3,6-Bis(trifluoromethanesulfonyloxy)phthalonitrile (0.5 g, 1.18 mmol) and anhydrous lithium chloride (0.13 g, 3 mmol) were dissolved in dry DMF (3 ml) under argon. 1-Decene (0.50 g, 3.6 mmol), tetrakis(triphenylphosphine)palladium(0) (72 mg, *ca.* 5mol%) and 2,6-lutidine (0.5 ml) were added at 10 minute intervals, and the reaction was heated at 100°C for 16 hours. The reaction was cooled, poured into excess water (40 ml), and extracted with ethyl acetate (3 x 20 ml). The combined organics were washed with 5% NaOH (20 ml), 5% HCl (20 ml) and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude black tar was purified by column chromatography over silica (eluent: petrol/CH_2Cl_2 1:1 → 0:1). The first fraction afforded triphenylphosphine and the second fraction afforded *3,6-bis(1'-decenyl)phthalonitrile* (0.04 g, 8.4%).

Preparation of non-mixed phthalocyanines (V) from the above phthalonitriles (IV):

Preparation of 1,4,8,11,15,18,22,25-octakis(1,1-H-2,2-H-perfluorodecyl)phthalocyanine:

3,6-Bis(1,1-H-2,2-H-perfluorodecyl)phthalonitrile (0.5g, 0.5mmol) was refluxed in DMAE (10ml) for 1 hour under a constant flow of NH_3 gas. After that time, zinc acetate dihydrate (99.999%, 36mg, 0.33eq.) was added and reflux continued for 24 hours. After cooling, the solvent was removed under reduced pressure. The solid residue was washed with methanol then chromatographed on silica (eluent: trifluorotoluene). A green fraction was isolated and *1,4,8,11,15,18,22,25-octakis(1,1-H-2,2-H-perfluorodecyl)phthalocyanine* recrystallised from trifluorotoluene (130mg, 25%) [^{1}H NMR (270 MHz, C_6F_6+2%C_6D_6, 50°C) δ 8.04 (s, 8H), 5.15 (t, 16H), 3.21 (m, 16H) ppm].

Preparation of 1,4,8,11,15,18,22,25-octakis(decylsulfanyl)phthalocyaninato magnesium(II):

A solution of 3,6-bis(decylsulfanyl)phthalonitrile (0.3g, 0.64mmol) was heated to reflux in dry pentanol (3ml) under nitrogen. DBU (0.07g, 0.46mmol) was added and the reaction heated for 1 hour. Anhydrous magnesium chloride (18.2mg, 0.19mmol) was added, and the reaction heated for a further 20 hours. The reaction was cooled and the

solvents removed under reduced pressure. The residue was purified by column chromatography over silica (eluent: DCM/Et_3N 100:1) and the first brown/red fraction collected and concentrated. The crude product was triturated with hot methanol (3 x 10ml) to remove yellow coloured impurities and recrystallised from THF/methanol to afford *1,4,8,11,15,18,22,25-octakis(decylsulfanyl)phthalocyaninato magnesium(II)* (0.21 g, 69.0%) [Found: C, 70.36; H, 9.38; N, 5.77. $C_{112}H_{176}N_8S_8Mg$ requires: C, 70.23; H, 9.26; N, 5.85. ^1H NMR (270 MHz, C_6D_6 containing 1% pyr-d_5, 50°C) δ 7.86 (s, 8H), 3.38 (t, 16H, J = 7.4 Hz), 2.05 (quint, 16H, J = 7.4 Hz), 1.68-1.58 (m, 16H), 1.52-1.26 (m, 96H), 0.90 (t, 24H, J = 6.6 Hz) ppm. λ_{max} (abs.) 776 nm (THF); λ_{max} (em.) 793 nm (THF)].

The following were prepared similarly:

1,4,8,11,15,18,22,25-Octakis(nonylsulfanyl)phthalocyaninato magnesium(II) [yield: 62.2%. Found: C, 69.44; H, 8,76; N, 5.99. $C_{104}H_{160}N_8S_8Mg$ requires: C, 69.27; H, 8.94; N, 6.21. ^1H NMR (270 MHz, C_6D_6 containing 1% pyr-d_5, 50°C) δ 7.86 (s, 8H), 3.38 (t, 16H, J = 7.25 Hz), 2.04 (quint, 16H, J = 7.4 Hz), 1.67-1.59 (m, 16H), 1.52-1.18 (m, 80H), 0.90 (t, 24H, J = 6.9 Hz) ppm. λ_{max} (abs.) 772 nm (THF); λ_{max} (em.) 796.8 nm (THF)].

1,4,8,11,15,18,22,25-Octakis(octylsulfanyl)phthalocyaninato magnesium(II) [yield: 48.3%. Found: C, 68.29; H, 8.69; N, 6.50. $C_{96}H_{144}N_8S_8Mg$ requires: C, 68.18; H, 8.58; N, 6.63. ^1H NMR (270 MHz, C_6D_6 containing 1% pyr-d_5, 50°C) δ 7.86 (s, 8H), 3.37 (t, 16H, J = 7.4 Hz), 2.03 (quint, 16H, J = 7.4 Hz), 1.68-1.57 (m, 16H), 1.52-1.25 (m, 64H), 0.91 (t, 24H, J = 6.8 Hz) ppm. λ_{max} (abs.) 774 nm (THF); λ_{max} (em.) 794 nm (THF)].

1,4,8,11,15,18,22,25-Octakis(heptylsulfanyl)phthalocyaninato magnesium(II) [yield: 7.4%. Found: C, 68.29; H, 8.69; N, 6.50. $C_{88}H_{128}N_8S_8Mg$ requires: C, 66.97; H, 8.18; N, 7.10. ^1H NMR (270 MHz, C_6D_6 50°C) δ 7.84 (s, 8H), 3.35 (t, 16H, J = 7.4 Hz), 2.02 (quint, 16H, J = 7.4 Hz), 1.6 (m, 16H), 1.315 (m, 48H), 0.89 (t, 24H, J = 6.6 Hz) ppm].

1,4,8,11,15,18,22,25-Octakis(hexylsulfanyl)phthalocyaninato magnesium(II) [yield: 66.7%. Found: C, 65.51; H, 7.60; N, 7.64. $C_{80}H_{112}N_8S_8Mg$ requires: C, 65.52; H, 7.70; N, 7.64. ^1H NMR (270 MHz, C_6D_6 containing 1% pyr-d_5, 50°C) δ 7.83 (s, 8H), 3.34 (t, 16H, J

= 7.25 Hz), 2.00 (quint, 16H, J = 7.5 Hz), 1.65-1.57 (m, 16H), 1.45-1.25 (m, 32H), 0.89 (t, 24H, J = 6.9 Hz) ppm. λ_{max} (abs.) 773 nm; λ_{max} (em.) 792 nm (THF)].

Preparation of 1,4,8,11,15,18,22,25-octakis(nonylsulfanyl)phthalocyanine:

1,4,8,11,15,18,22,25-Octakis(nonylsulfanyl)phthalocyaninato magnesium(II) (50mg) was dissolved in trifluoroacetic acid (4ml) and stirred at room temperature under argon for 2 hours. The reaction was poured into water/ice (80ml) and extracted with DCM (2x50 ml). The DCM extract was washed with 5% NaOH (40ml), brine (40ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was further purified by column chromatography over silica (eluent: DCM/Et_3N 99:1). The first fraction was collected and recrystallised from THF/acetone to afford *1,4,8,11,15,18,22,25-octakis(nonylsulfanyl)phthalocyanine* [Found: C, 70.06; H, 9.20; N, 6.12. $C_{104}H_{162}N_8S_8$ requires: C, 70.14; H, 9.17; N, 6.29. ^{1}H NMR (270 MHz, C_6D_6 containing 1% pyr-d_5, 50°C) δ 7.70 (s, 2H), 3.21 (t, 16H, J = 7.25 Hz), 1.92 (quint, 16H, J = 7.4 Hz), 1.66-1.55 (m, 16H), 1.50-1.24 (m, 80H), 0.91 (t, 24H, J = 6.9 Hz), 0.07 (s, 2H) ppm].

Preparation of 1,4,8,11,15,18,22,25-octakis(dodecylsulfanyl)phthalocyanine:

3,6-(Dodecylsulfanyl)phthalonitrile (0.21 g, 0.40 mmol) was heated to reflux in DMAE (10 ml) under the continual passage of ammonia gas. After 2 hours at reflux, lithium chloride (19.8 mg, 0.48 mmol) was added. Reflux under the continual passage of ammonia gas was continued for 20 hours. The reaction was cooled and the solvent removed under reduced pressure. The residue was stirred in glacial acetic acid (10 ml) for 30 minutes, resulting in a bright red coloration. The acetic acid was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 and washed with sat. Na_2CO_3, sat. NH_4Cl, brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was further purified by column chromatography over silica (eluent: CH_2Cl_2:Et_3N 100:1). The first red/brown fraction was collected and concentrated under reduced pressure. The resulting purple solid was recrystallised from THF/acetone to afford *1,4,8,11,15,18,22,25-octakis(dodecylsulfanyl)phthalocyanine* (44.1mg) [m.p. 88-88.5°C. Found: C, 72.53; H, 9.97; N, 5.29. $C_{128}H_{210}N_8S_8$ requires C, 72.60; H, 10.00; N, 5.29. λ_{max} (toluene) 797 nm.].

Preparation of mixed phthalocyanines from the above phthalonitriles:

Preparation of 1,4-bis(3-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine:

3,6-Bis(3-methoxyphenyl)phthalonitrile (0.33 g, 0.97 mmol) and 3,6-didecylphthalonitrile (3.57 g, 8.73 mmol) were dissolved in pentanol (30 ml) and heated to reflux. Lithium metal (0.4 g, 6 eq.) was added in portions and refluxing was continued for 6 hours. After cooling, glacial acetic acid (40 ml) was added and the mixture stirred at room temperature for 1 hour. The solvents were removed under reduced pressure and the resultant slurry was triturated with methanol and filtered. The resulting green solid was chromatographed over silica gel (eluent: petroleum ether/dichloromethane 9:1). 1,4,8,11,15,18,22,25-octakis(decyl)phthalocyanine was removed (0.98 g), the eluent changed to petroleum ether/dichloromethane 7:3 and *1,4-bis(3-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine* was isolated (18 mg, 2%) [Found: C, 81.17; H, 9.61; N, 6.83%. $C_{106}H_{150}N_8O_2$ requires: C, 81.18; H, 9.64; N, 7.14%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.14-7.94 (m, 16H), 4.39 (t, 8H, J 7), 3.84 (s, 6H), 3.16 (t, 4H, J 7), 2.1 (m, 6H), 0.72-1.1 (m, 108H), 0.33 (s, 2H) ppm].

Investigation of routes A and B:

Preparation of 4,5-dibromo-3,6-dihydroxyphthalonitrile:

To a stirred solution of 2,3-dicyanohydroquinone (3 g, 18.7 mmol) in *tert*-butanol (12 ml) at 45°C was added NBS (7 g, 38.8 mmol) portionwise over 15 minutes. Stirring was continued for 2 hours and then additional NBS (7 g, 38.8 mmol) was added over 15 minutes. After a further 2 hours, the reaction was cooled to room temperature and poured into an aqueous solution of sodium metabisulfite (6 g in 60 ml, excess) at 0°C with vigorous stirring. The mixture was stirred for 10 minutes, the precipitate filtered, and washed with cold water (30 ml). The product was dried under vacuum at 60°C for 24 hours to yield *4,5-dibromo-3,6-dihydroxyphthalonitrile* as a cream powder (3.94 g, 66.1%). This was used without further purification, but an analytical sample was prepared by recrystallisation from acetone/water [m.p. 248°C (dec.). Found C, 30.47; H, 0.42; N, 8.70; Br, 50.22. $C_8H_2N_2O_2Br_2$ (317.92) requires C, 30.22; H, 0.63; N, 8.81; Br 50.27. ^{13}C NMR (270 MHz, acetone-d_6) δ 151.74 (C-O), 123.08 (C-Br), 113.07 (CN), 102.46 (C-CN) ppm. ν_{max} (nujol) 3250 (br), 2232 (m) cm^{-1}.].

Preparation of 4,5-dibromo-3,6-dibutoxyphthalonitrile:

A mixture of 4,5-dibromo-3,6-dihydroxyphthalonitrile (2.50 g, 7.86 mmol), triphenylphosphine (4.95 g, 18.9 mmol) and 1-butanol (1.5 g, 20.2 mmol) was dissolved in dry THF (80 ml) and cooled to 0°C. A solution of diisopropyl azodicarboxylate (4.35 g, 21.5 mmol) in THF (30 ml) was added dropwise over 30 minutes. The solution was allowed to warm to room temperature and stirred for an additional 10 hours. The THF was removed under reduced pressure to give a dark red oil, which was dissolved in diethyl ether (20 ml). The solution was filtered to remove undissolved triphenylphosphine oxide, concentrated and separated by column chromatography over silica (eluent: CH_2Cl_2/petrol 1:2). The product was recrystallised from cyclohexane to afford *4,5-dibromo-3,6-dibutoxyphthalonitrile* as white crystals (2.75 g, 83.6%) [m.p. 72-73°C. Found C, 44.51; H, 4.28; N, 6.47; Br, 37.33. $C_{16}H_{18}N_2O_2Br_2$ (430.14) requires C, 44.68; H, 4.22; N, 6.51; Br, 37.15. ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.24 (t, J = 6.4 Hz, 4H), 1.92 (quint, J = 7.0 Hz, 4H), 1.67-1.53 (m, 4H), 1.04 (t, J = 7.3 Hz, 6H) ppm. ^{13}C NMR (270 MHz, $CDCl_3$) δ 156.37 (ArC-O), 129.61 (ArC-Br), 112.33 (CN), 109.22 (ArC-CN), 76.43, 31.95, 18.92, 13.73 ppm. ν_{max} (nujol) 2230 (m) cm^{-1}. MS (70 eV, EI): *m/z* (%): 432 (3.1), 430 (5.2), 428 (3.5) [M$^+$].].

Preparation of 4-bromo-3,6-dibutoxyphthalonitrile:

A mixture of 4,5-dibromo-3,6-dihydroxyphthalonitrile (3 g, 9.4 mmol), finely crushed potassium carbonate (3 g, excess) and TBAB (0.26 g, 0.7 mmol) was refluxed in MEK (80 ml) for 12 hours. The reaction was cooled and 1-iodobutane (3.70 g, 20 mmol) was added. Reflux was continued for a further 72 hours. Upon cooling, the reaction was filtered and washed with ethyl acetate. The organics were removed under reduced pressure and the residue dissolved in ethyl acetate (100 ml). This was washed with 5% HCl (25 ml), sat. K_2CO_2 (25 ml), water (25 ml), brine (25 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography over silica (eluent: petrol/CH_2Cl_2 2:1) and recrystallised from cyclohexane to afford *4-bromo-3,6-dibutoxyphthalonitrile* (1.43 g, 43%) [m.p. 102.5-104°C. Found C, 54.71; H, 5.43; N, 7.89; Br, 22.67. $C_{16}H_{19}N_2O_2Br_1$ (351.24) requires C, 54.85; H, 5.47; N, 8.00; Br, 22.54. ^{1}H NMR (270 MHz, acetone-d_6) δ 7.88 (s, 1H), 4.30 (t, 2H, J = 6.4 Hz), 4.18 (t, 2H, J = 6.4 Hz), 1.86 (m, 4H), 1.56 (m, 4H), 1.00 (t, 3H, J = 7.3

Hz), 0.99 (t, 3H, J = 7.3 Hz) ppm. ^{13}C NMR (300 MHz, acetone-d_6) δ 157.68 (ArC-O), 152.80 (ArC-O), 124.94, 123.33 (ArC-H), 112.81 (CN), 112.69 (CN), 111.39 (Ar*C*-CN), 103.83 (Ar*C*-CN), 75.75, 70.40, 31.81, 30.57, 18.70, 18.66, 13.07, 12.98 ppm. ν_{max} (nujol) 2230 (m) cm^{-1}. MS (70 eV, EI): *m/z* (%): 350.1 (4.8), 352.1 (4.5) [M$^+$].].

Preparation of 2-(4-pyridyl)-4,4,5,5-tetramethyl-1,3-dioxaborolane:

To a cold slurry at -78°C of 4-iodopyridine (5g, 24mmol) in dry diethylether (250ml) was added *n*-butyllithium (2.5M in hexanes, 12ml, 30.1mmol) slowly. After 20 minutes, tributoxyboron (6.9g, 30.1mmol) was added and the temperature was allowed to rise to room temperature over 2 hours. Pinacol (3.8g, 32.3mmol) was added followed, 10 minutes later, by glacial acetic acid (1.47g, 24.6mmol). The mixture was filtered through celite, the filter washed with diethylether (100ml) and the combined organics were reduced under vacuum. The crude product was recrystallised from cyclohexane yielding a white solid, 3.14g (15.4mmol, 64%). [mp. 150-152°C (Lit. (C. Coudret, Synthetic Commun., 1996, vol. 26, page 3543) 151°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, 2H, J=6Hz), 7.65 (d, 2H, J=6Hz), 1.38 (s, 12H) ppm].

Preparation of 4-pyridyl-3,6-dibutoxyphthalonitrile:

Cesium fluoride (0.66g, 4.4mmol), tetrakis(triphenylphosphine)palladium(0) (0.25g, 10mol%) and 2-(4-pyridyl)-4,4,5,5-tetramethyl-1,3-dioxaborolane (0.45g, 2.2mmol) were placed under nitrogen for 10 minutes. 4-Bromo-3,6-dibutoxyphthalonitrile (0.38g, 1.1mmol) in 1,2-dimethoxyethane (DME) (20ml) was added and the mixture was refluxed for 48 hours, adding fresh tetrakis(triphenylphosphine)palladium(0) catalyst (0.25g, 10mol%) every 24 hours. After cooling, water (50ml) was added and the organics were extracted with diethylether (100ml), washed with brine and dried ($MgSO_4$). The drying agent was filtered off and the solvent was removed under reduced pressure to leave a solid which was recrystallised from cyclohexane as white needles, 0.2g (0.6mmol, 53%). [mp. 150-151°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, 2H), 7.46 (d, 2H), 7.13 (s, 1H), 4.12 (t, 2H), 3.71 (t, 2H), 1.85 (qn, 2H), 1.48-1.6 (m, 4H), 1.39 (m, 2H), 1.02 (t, 3H), 0.83 (t, 3H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.79 (ar.C-O), 153.4 (ar.C-O), 150.58 (2xpyr.C), 143.49 (ar.C-pyr), 139.63 (2xpyr.C), 123.55 (2x CN), 118.88 (ar.CH), 113.23 (ar.C-CN), 112.76 (ar.C-CN), 112.23 (pyr.C-ar), 76.28, 70.30, 31.86, 30.9, 19.08, 18.81, 13.73, 13.58 ppm].

Preparation of 4-(2-thienyl)-3,6-dibutoxyphthalonitrile:

4-Bromo-3,6-dibutoxyphthalonitrile (0.5g, 1.42mmol) and tetrakis(triphenylphosphine)palladium(0) (0.16g, 10mol%) were stirred in DME (20ml) under N_2 for 10 minutes. 2-Thiopheneboronic acid (0.27g, 2.1mmol) was added, followed by a 2M aqueous solution of Na_2CO_3 (2ml). The mixture was brought to reflux for 12 hours. After cooling, a saturated solution of K_2CO_3 (100ml) was added and the organics were extracted with diethylether (2x100ml), washed with aq. 5% HCl (100ml), water (100ml), brine and dried ($MgSO_4$). The drying agent was filtered off and the solvent was removed under reduced pressure to leave an orange solid. This was recrystallised from cyclohexane as pale yellow crystals, 0.31g (0.88mmol, 62%). [^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, 1H), 7.45 (d, 1H), 7.34 (s, 1H), 7.16 (qn, 1H), 4.13 (t, 2H), 3.96 (t, 2H), 1.77-1.9 (m, 4H), 1.43-1.61 (m, 4H), 1.0 (t, 3H), 0.94 (t, 3H) ppm].

Preparation of 4-phenyl-3,6-dibutoxyphthalonitrile:

4-Bromo-3,6-dibutoxyphthalonitrile (0.6g, 1.7mmol) and tetrakis(triphenylphosphine)palladium(0) (0.19g, 10mol%) were stirred in DME (50ml) under N_2 for 10 minutes. Phenylboronic acid (0.23g, 1.87mmol) was added, followed by a 2M aqueous solution of Na_2CO_3 (2ml). The mixture was brought to reflux for 12 hours. After cooling, a saturated solution of K_2CO_3 (100ml) was added and the organics were extracted with diethylether (2x100ml), washed with aq. 5% HCl (100ml), water (100ml), brine and dried ($MgSO_4$). The drying agent was filtered off and the solvent was removed under reduced pressure to leave an orange solid. This was recrystallised from cyclohexane as pale orange crystals, 0.38g (1.09mmol, 64%). [^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.54 (m, 6H), 7.13 (s, 1H), 4.11 (t, 2H), 1.84 (qn, 4H), 1.49-1.6 (m, 4H), 1.29 (m, 2H), 1.01 (t, 3H), 0.78 (t, 3H) ppm].

Preparation of 4,5-diphenyl-3,6-dibutoxyphthalonitrile:

4,5-Dibromo-3,6-dibutoxyphthalonitrile (0.5g, 0.16mmol) and tetrakis(triphenylphosphine)palladium(0) (0.13g, 10mol%) were stirred under N_2 for 10 minutes in DME (20ml). Phenylboronic acid (0.31g, 2.55mmol) followed by a 2M aqueous solution of Na_2CO_3 (2ml) were added and the mixture brought to reflux. The reaction was followed

by TLC (eluent: ethylacetate-hexane 1:3). One more eq. of tetrakis(triphenylphosphine)palladium(0) (0.13g, 10mol%) was added after 24 hours and reflux continued for a further 12 hours. After cooling, water (100ml) was added and the product was extracted with diethylether (3x100ml). The organic phase was washed with brine and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent was removed under reduced pressure. The product was recrystallised from cyclohexane as yellow crystals, 130mg (0.4mmol, 34%). [^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.23 (m, 6H), 6.97-7.03 (m, 4H), 3.56 (t, 4H), 1.44 (qn, 4H), 1.14 (m, 4H), 0.72 (t, 6H) ppm].

Preparation of 3,6-dibutoxy-4,5-di(4-pyridyl)phthalonitrile:

A mixture of 4,5-dibromo-3,6-dibutoxyphthalonitrile (89 mg, 0.208 mmol), pyridine-4-boronic acid (100 mg, 0.832 mmol), cesium fluoride (250 mg, 1.64 mmol) and tetrakis(triphenylphosphine)palladium(0) (24 mg, 10 mol%) was placed under nitrogen for 15 minutes. Dry DME (20 ml) was then added. The resulting mixture was brought to reflux for 18 hours under argon. TLC analysis showed two separable spots. The mixture was filtered and the solvent was evaporated under reduced pressure. The resulting products were purified by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C)/THF 1:1). The first fraction was collected and identified as 3,6-dibutoxy-4-(4-pyridyl)phthalonitrile. The polarity of the eluent was then increased (petroleum ether (b.p. 40-60°C)/THF 3:7) to isolate *3,6-dibutoxy-4,5-di(4-pyridyl)phthalonitrile* which was recrystallised from cyclohexane to yield light pink crystals (40 mg, 45%) [mp. 206-208°C. Found: C, 72.86; H, 6.12; N, 12.91%. $C_{26}H_{26}N_4O_2$ requires: C, 73.22; H, 6.14; N, 13.14%. m/e 426 (M^+, 14.44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, 4H, J 4.5), 6.98 (d, 4H, J 4.4), 3.78 (t, 4H, J 6.3), 1.46 (quintet, 4H, J 6.5), 1.17 (quintet, 4H, J 7.2), 0.75 (t, 6H, J 7.3) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 156, 149.7, 141.2, 139.4, 124.6, 112.8, 110.7, 76.1, 31.7, 18.6, 13.4 ppm].

Preparation of 4-(*p*-N,N-dimethylaminophenyl)-3,6-dibutoxyphthalonitrile:

4-Bromo-3,6-dibutoxyphthalonitrile (0.5g, 1.42mmol) and tetrakis(triphenyl)-phosphine palladium(0) (0.2g, 10mol%) was dissolved in dry DME (20ml) and left to stir under N_2 for 30 minutes. 4-(N,N-Dimethylaminophenyl)boronic acid (0.4g 2.84mmol) was added followed by 2M Na_2CO_3 (2ml) solution. The reaction was brought to reflux for 16 hours and then allowed to cool to room temperature. The product was partitioned

between water (100ml) and ether (100ml). The ether layer was washed with brine (2x100ml) and dried over $MgSO_4$. The ether was filtered and reduced yielding a yellow solid which was purified by column chromatography (ethyl acetate: hexane, 3:1) and recrystallised from cyclohexane to afford *4-(p-N,N-dimethylaminophenyl)-3,6-dibutoxyphthalonitrile* (0.3g, 0.76mmol, 53.9%) as yellow fluffy crystals [^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 2H), 7.09 (s, 1H), 6.78 (d, 2H), 4.09 (t, 2H), 3.65 (t, 2H), 3.04 (s, 6H), 1.83 (pent, 2H), 1.15 (pent, 4H), 1.34 (sex, 2H), 0.98 (t, 3H), 0.84 (t, 3H) ppm].

Preparation of 3,6-dibutoxy-4-*p*-methoxyphenylphthalonitrile:

4-Bromo-3,6-dibutoxyphthalonitrile (0.5g, 1.42mmol) and tetrakis(triphenyl)-phosphine palladium(0) (0.2g, 10mol%) was dissolved in dry DME (20ml) and left to stir under N_2 for 30 minutes. 4-*p*-Methoxyphenylboronic acid (0.43g, 2.84mmol) was added followed by 2M Na_2CO_3 (2ml) solution. The reaction was brought to reflux for 16 hours and then allowed to cool to room temperature. The product was partitioned between water (100ml) and ether (100ml). The ether layer was washed with brine (2x100ml) and dried over ($MgSO_4$). The ether was filtered and reduced yielding a brown solid, crude yield 0.31g, which was purified by column chromatography (ethyl acetate) and recrystallised from cyclohexane to afford *3,6-dibutoxy-4-p-methoxyphenylphthalonitrile*. [^{1}H NMR (300MHz, $CDCl_3$) δ 7.67 (d, 2H), 7.17 (s, 1H), 7.04 (d, 2H), 4.11 (t, 2H), 3.63 (t, 2H), 3.03 (s, 6H), 1.81 (p, 2H), 1.13 (p, 4H), 1.31 (sex, 2H), 0.96 (t, 3H), 0.83 (t, 3H) ppm].

Preparation of 3,6-dibutoxy-4-carboxyphenylphthalonitrile:

4-Bromo-3,6-dibutoxyphthalonitrile (0.25g, 0.7mmol), tetrakis(triphenyl)phosphine palladium(0) (0.1g, 10mol%), cesium carbonate (0.92g, 5.69mmol) and para-carboxylic acid-boronic acid (0.23g, 1.42mmol) were placed under N_2 for 1 hour. Toluene:ethanol:water 3:3:1 (21ml) was added and the reaction brought to reflux for 12 hours. On cooling the mixture was acidified with conc. HCl (20ml) and extracted with DCM (2x100ml). The combined organic layers were dried over $MgSO_4$, filtered and reduced yielding a yellow solid which was recrystallised from ethanol to afford *3,6-dibutoxy-4-carboxyphenylphthalonitrile* (0.06g, 0.168mmol, 24%). [^{1}H NMR (300MHz, $CDCl_3$) δ 8.23 (d, 2H), 7.67 (d, 2H), 7.16 (s, 1H), 4.08 (t, 2H), 3.64 (t, 2H), 3.05 (s, 6H), 1.84 (p, 2H), 1.15 (p, 4H), 1.33 (sex, 2H), 0.94 (t, 3H), 0.85 (t, 3H) ppm].

Preparation of 4-*p*-aminophenyl-3,6-dibutoxyphthalonitrile:

4-Bromo-3,6-dibutoxyphthalonitrile (0.05g, 0.142mmol), tetrakis(triphenyl)-phosphine palladium(0) (0.02g, 10 mol %), caesium carbonate (0.09g, 0.569mmol) and *p*-aminophenyl boronic acid (0.06g 0.284mmol) were placed under N_2 for 1 hour. Dry DME (10ml) was added and the reaction brought to reflux for 12 hours. The product was partitioned between ether (20ml) and water (20ml). The organics were dried over $MgSO_4$, filtered and reduced yielding a yellow solid, crude yield 0.021g which was recrystallised from ethanol to afford *4-p-aminophenyl-3,6-dibutoxyphthalonitrile.* [^{1}H NMR (300MHz, $CDCl_3$) δ 7.38 (d, 2H), 7.17 (s, 1H), 6.75 (d, 2H), 4.07 (t, 2H), 3.62 (t, 2H), 3.07 (s, 6H), 1.85 (p, 2H), 1.16 (p, 4H), 1.32 (sex, 2H), 0.93 (t, 3H), 0.84 (t, 3H) ppm].

Preparation of 4-(*p*-hydroxymethylphenyl)-3,6-dibutoxyphthalonitrile:

A mixture of 4-(hydroxymethyl)benzeneboronic acid (500 mg, 3.311 mmol), 4-bromo-3,6-dibutoxyphthalonitrile (764 mg, 2.17 mmol), triphenylphosphine (85.7 mg, 0.327 mmol), palladium chloride (42.8 mg, 0.241 mmol), and Na_2CO_3 (50 mg) was placed under nitrogen for 30 minutes. The solvent (35 ml), consisting of toluene, ethanol and water, 3:3:1 respectively was then added. The mixture was refluxed for 24 hours under N_2. The solvent was then removed under reduced pressure and the mixture redissolved in dichloromethane (50ml) and filtered through celite to remove palladium residues. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica (eluent: dichloromethane:ethylacetate, 9:1) to give *4-(p-hydroxymethylphenyl)-3,6-dibutoxyphthalonitrile* (700mg, 1.85mmol, 85%). [^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 2H, J= 8.4Hz), 7.48 (d, 2H, J= 8.4Hz), 7.12(s, 1H), 4.80 (s, 2H), 4.11 (t, 2H, J= 6.5Hz), 3.64 (t, 2H, J= 6.4Hz), 1.84(qn, 2H, J= 6.6Hz), 1.47-1.58 (m, 4H),1.26 (qn, 2H, J= 7.3Hz), 0.98 (t, 3H, J= 7.4Hz), 0.80 (t, 3H, J= 7.4Hz) ppm. Found: C, 72.82; H, 6.93; N, 7.22%. $C_{23}H_{26}N_2O_3$ requires: C, 73.01; H, 6.88; N; 7.41%].

Preparation of 4-(*p*-methanesulfonyloxymethylphenyl)-3,6-dibutoxyphthalonitrile:

4-(*p*-Hydroxymethylphenyl)-3,6-dibutoxyphthalonitrile (100mg, 0.26mmol) was dissolved in DCM (30ml) containing triethylamine (30mg, 0.29mmol). The reaction mixture was cooled to 0°C and stirred. Methanesulfonylchloride (33mg, 0.29mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 2 hours, and then washed with 10% HCl (2x25 ml) and brine (25ml), and dried

($MgSO_4$). The mixture was filtered and the solvent removed under vacuum to yield a yellow oil. The oil was chromatographed (silica gel; eluent: DCM) to obtain *4-(p-methanesulfonyloxymethylphenyl)-3,6-dibutoxyphthalonitrile* (85 mg, 70%) [Found: C, 62.97; H, 6.13; N, 6.10. $C_{24}H_{28}N_2O_5S$ requires C, 63.15; H, 6.14; N, 6.14%. ^{1}H-NMR ($CDCl_3$) δ 7.59 (2H, d, J 8.2), 7.54 (2H, d, J 8.2), 7.14 (1H, s), 5.31 (2H, s), 4.12 (2H, t, J 6.3), 3.65 (2H, t, J 6.4), 3.04 (3H, S), 1.85 (2H, quint, J 6.6), 1.48-1.60 (4H, m),1.27 (2H, quint, J 7.2), 0.99 (3H, t, J 7.3), 0.79 (3H, t, J 7.4)].

Preparation of 4-*p*-[(O-tyrosinyl methyl ester)oxymethylphenyl]-3,6-dibutoxy-phthalonitrile:

A mixture of 4-(*p*-methanesulfonyloxymethylphenyl)-3,6-dibutoxyphthalonitrile (500mg, 1.08mmol), Dl-*p*-Tyrosine (318mg, 1.63mmol), K_2CO_3 (600mg, excess) and tris(3,6-dioxaheptyl)amine (TDA-1, Aldrich) (50mg, 0.154mmol) in MEK (30ml) as solvent was stirred under Ar at reflux for 48 hours. After cooling the solid was filtered off and washed with DCM. The solution was evaporated off under reduced pressure to leave a yellow oil which was purified by column chromatography (silica gel, eluent: DCM:ethylacetate, 2:3) to yield *4-p[(O-tyrosinyl methyl ester)oxymethylphenyl]-3,6-dibutoxyphthalonitrile* (210 mg, 34%) [^{1}H-NMR ($CDCl_3$) δ 7.55 (4H, s), 7.11-7.14 (3H, m), 6.93 (2H, d, *J* 8.7), 5.12 (2H, s), 4.11 (2H, t, *J* 6.4), 3.65 (2H, t, *J* 6.3), 3.68-3.75 (4H, m), 3.06 (1H, dd, *J* 4.1 and 13.5), 2.84 (1H, dd, *J* 7.7 and 13.5), 1.21-1.86(10H, bm), 0.98 (3H, t, *J* 7.4), 0.79 (3H, t, *J* 7.4)].

Preparation of 3,6-di(butyloxy)-4-(4'-ethoxy-4'-oxobutyl)phthalonitrile:

A mixture of triphenylphosphine (250mg, 0.95mmol), lithium chloride (0.6g, 14mmol) and bis(triphenylphosphine)nickel (II) chloride (313mg, 0.5mmol) was stirred in dry THF (10ml) under nitrogen for 10 minutes. *n*-BuLi (2.5M in hexanes, 0.4ml) was added to the blue solution at room temperature. The solution turns deep red. Solid 3,6-bis(butyloxy)-4-bromophthalonitrile (3.5g, 10mmol) was added at once under a fast stream of nitrogen and the pale brown solution was cooled to -78°C. 4-Ethoxy-4-oxobutylzinc bromide (0.5M in THF purchased from Aldrich, (20ml, 10mmol)) was added via a syringe. The solution was allowed to warm to room temperature and stirring continued for 12 hours under nitrogen. 5% HCl (50ml) was added and the mixture extracted with ethyl acetate (3x20ml). The combined organics were washed with 5% HCl (10ml), 5% NaOH (10ml),

brine (10ml), and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica [eluent: petroleum ether (bp. 40-60°C): dichloromethane 1:1] to remove triphenylphosphine. The eluent was changed to dichloromethane. A fluorescent fraction eluted. This proved to be 3,6-dibutyloxyphthalonitrile by ^{1}H-NMR spectroscopy (570mg, white powder). Another fluorescent fraction eluted which was not identified. Finally, *3,6-di(butyloxy)-4-(4'-ethoxy-4'-oxobutyl)phthalonitrile* (1.9g, 4.9mmol, 49%) was obtained in the last eluting fraction as a pale yellow oil which solidifies on standing [mp 43-48°C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.0 (s, 1H), 4.1 (q, 2H), 4.04 (m, 4H), 2.69 (t, 2H), 2.31 (t, 2H), 1.9 (m, 2H), 1.78 (m, 4H), 1.5 (m, 4H), 1.24 (t, 3H), 0.95 (m, 6H) ppm. m/z. 386 (M, 14.9%)].

Preparation of 3,6-bis(butyloxy)-4-(4'-chlorobutyl)phthalonitrile:

A mixture of triphenylphosphine (125mg, 0.5mmol), lithium chloride (0.3g, 7mmol) and bis(triphenylphosphine)nickel (II) chloride (156mg, 0.24mmol) was stirred in dry THF (5ml) under nitrogen for 10 minutes. *n*-BuLi (2.5M in hexanes, 0.2ml) was added to the blue solution at room temperature. The solution turns deep red. Solid 3,6-bis(butyloxy)-4-bromophthalonitrile (1.4g, 4mmol) was added at once under a fast stream of nitrogen and the pale brown solution was cooled to -78°C. 4-Chlorobutylzinc bromide (0.5M in THF purchased from Aldrich, (10ml, 5mmol)) was added via a syringe. The solution was allowed to warm to room temperature and stirring continued for 12 hours under nitrogen. 5% HCl (20ml) was added and the mixture extracted with ethyl acetate (3x10ml). The combined organics were washed with 5% HCl (10ml), 5% NaOH (10ml), brine (10ml), and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent removed under reduced pressure. The residue was purified by column chromatography over silica [eluent: petroleum ether (bp. 40-60°C): dichloromethane, 1:1] to remove triphenylphosphine. A second fraction was collected which proved to be unreacted starting material (0.9g). The eluent was changed to dichloromethane to obtain *3,6-bis(butyloxy)-4-(4'-chlorobutyl)phthalonitrile* (200mg, 0.55mmol, 14% or 39% based on recovered starting material) as a pale yellow oil which solidifies on standing [^{1}H NMR (270 MHz, $CDCl_3$) δ 7.19 (s, 1H), 4.8 (t, 2H), 4.6 (t, 2H), 3.59 (t, 2H), 2.7 (t, 2H), 1.82 (m, 8H), 1.45-1.6 (m, 4H), 0.95-1.03 (m, 6H) ppm. m/z. 362 (M, 1.6%), 364 (M+2, 0.53%)].

Preparation of 3,6-dibutoxy-4,5-(tris(isopropyl)silylethynyl)phthalonitrile:

A solution of 4,5-dibromo-3,6-dibutoxyphthalonitrile (1.00g, 2.33mmol) was dissolved in freshly distilled triethylamine (6ml). The solution was degassed by heating it briefly under argon. $PdCl_2(PPh_3)_2$ (0.164g, 10mol%) was added, followed by TIPS-acetylene (1.06g, 5.82mmol) and finally CuI (0.06g, 13mol%) at 10 minute intervals. The reaction was refluxed for 16 hours, cooled, filtered to remove palladium salts, washed with ethyl acetate and concentrated under reduced pressure. The crude product was purified by column chromatography over silica (eluent: petrol/DCM, 1:2) to afford *3,6-dibutoxy-4,5-(tris(isopropyl)silylethynyl)phthalonitrile* (0.82 g, 56%) after recrystallisation from ethanol [Found: C, 72.11; H, 9.37; N, 4.28. $C_{38}H_{60}O_2N_2Si_2$ requires C, 72.10; H, 9.55; N, 4.42. ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (t, 4H, J = 6.8 Hz), 1.83 (quint, 4H, J = 7.2 Hz), 1.56-1.45 (m, 4H), 1.2-1.08 (br s, 42H), 0.97 (t, 6H, J = 7.4 Hz) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 160.03, 127.13, 112.94, 109.05, 108.60, 98.43, 75.98, 31.94, 18.80, 15.58, 13.73, 11.28 ppm].

Preparation of 3,6-dibutoxy-4-(m-methoxyphenyl)phthalonitrile:

A mixture of 3-methoxybenzeneboronic acid (70 mg, 0.451 mmol), 4-bromo-3,6-dibutoxyphthalonitrile (107 mg, 0.304 mmol), triphenylphosphine (12 mg, 0.045 mmol), palladium chloride (6 mg, 0.033 mmol) and Na_2CO_3 (50 mg) was placed under nitrogen for 30 minutes. The solvent (15 ml), consisting of: toluene, ethanol, and water, 3:3:1 respectively, was then added. The mixture was refluxed for 24 hours under Ar. The solvent was evaporated, the mixture redissolved in DCM and filtered through celite to remove palladium residue. The solvent was evaporated and the resulting product was purified by column chromatography (silica gel, eluent: DCM/petrol 4:1) to give 3,6-dibutoxy-4-(m-methoxyphenyl)phthalonitrile (95 mg, 83%) [m.p. 91-92.2°C. Found: C, 72.67; H, 7.04; N, 7.18%; $C_{23}H_{26}N_2O_3$ requires: C, 72.99; H, 6.92; N, 7.40%. m/e 378 (M^+, 6.54), 379 (M^++1, 1.65). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (1H, d, J 8.2), 7.13 (1H, s), 7.10 (1H, m), 7.07 (1H, m), 7.00 (1H, dd, J 8.2 and 2.6), 4.10 (2H, t, J 6.4), 3.86 (3H, s), 3.64 (2H, t, J 6.3), 1.84 (2H, quint, J 6.3), 1.47-1.59 (4H, m), 1.26 (2H, quint, J 7.5), 0.98 (3H, t, J 7.4), 0.80 (3H, t, J 7.3) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 160, 157.7, 153.5, 142.4, 137, 130.1, 121.1, 119.5, 114.8, 114.6, 113.6, 113.2, 111.8, 103.6, 75.5, 70, 55.5, 31.9, 30.9, 19, 18.8, 13.7, 13.6 ppm].

Preparation of 3,6-dibutoxy-4,5-di(m-methoxyphenyl)phthalonitrile:

The procedure for the synthesis of 3,6-dibutoxy-4-(m-methoxyphenyl)-phthalonitrile above was followed using 4,5-dibromo-3,6-dibutoxyphthalonitrile (700 mg, 1.62 mmol) and 3-methoxybenzeneboronic acid (700 mg, 4.88 mmol). The resulting crude product was then purified by column chromatography (silica gel, eluent: DCM) to give 3,6-dibutoxy-4,5-di(m-methoxyphenyl)phthalonitrile (350 mg, 44%) [Found: C, 74.52; H, 6.67; N, 5.72%; $C_{30}H_{32}N_2O_4$ requires: C, 74.36; H, 6.66; N, 5.78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (2H, m), 6.76 (2H, dd, J 8.3 and 2.6), 6.61 (2H, dd, J 7.7 and 2.4), 6.54 (2H, dd, J 2.4 and 1.6), 3.65 (4H, t, J 6.5), 3.64 (6H, s), 1.45 (4H, quint, J 6.5), 1.17 (4H, quint, J 7.6), 0.74 (6H, t, J 7.3) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3 (ArC-O), 156.8 (ArC-O), 142.7 (ArC-O), 135, 129, 122.8, 115.6, 114.3 , 113.6, 109.8, 75.4 (-OCH_2), 55.3 (O-CH_3), 38.29, 31.8, 18.7, 13.55ppm].

Preparation of mixed phthalocyanines from route A:

Preparation of 1,4-dibutoxy-2-bromo-8,11,15,18,22,25-hexakis(decyl)phthalocyanine:

To dry *n*-butanol (10ml) was added lithium metal (60mg, 8.5mmol) and the mixture was heated until the lithium had reacted. The solution was cooled to room temperature. 3,6-Didecylphthalonitrile (350mg, 0.85mmol), 4-bromo-3,6-dibutoxyphthalonitrile (300mg, 0.85mmol), and tetrakis(triphenylphosphine)palladium(0) (49mg, 0.0425mmol, 5%mol) were added under N_2 and heated at 60°C for 12 hours in the dark. After cooling to room temperature, glacial acetic acid (2ml) was added and stirring was continued for 30 minutes. The solvent was removed under reduced pressure and the residue washed with methanol (3x50ml). The crude phthalocyanine mixture was separated by column chromatography over silica (eluent: petrol ether). The first fraction is 1,4,8,11,15,18,22,25-octakis(decyl)phthalocyanine (50mg) identical with an authentic sample. The eluent was then changed to petrol/CH_2Cl_2 (10:1) and a second fraction collected. This fraction was further purified by preparative scale TLC (eluent: petrol/CH_2Cl_2 (3:1)) and recrystallised from THF/methanol to afford *1,4-dibutoxy-2-bromo-8,11,15,22,25-hexakis(decyl)phthalocyanine* (150mg) as a dark green solid. [^{1}H NMR (300Mz, C_6D_6) δ 7.93 (s,1H), 7.91 (br s, 3H), 7.81 (s,2H), 7.75 (s,1H), 4.95-4.88 (m, 8H), 4.26 (t, 2H), 2.40-2.22 (m,14H), 2.15 (quint, 2H), 1.96 (br quint, 2H), 1.78-1.08 (m,

86H), 1.01 (t, 3H) ,1.00 (t, 3H), 0.91-0.75 (m, 18H), -0.35 (s, 2H). MALDI-MS: cluster centred at 1579. λ_{max} (abs.) 720, 648 nm (THF)].

Preparation of 1,4-dibutoxy-2-pyridyl-8,11,15,18,22,25-hexakis(decyl)phthalocyanine:

3,6-Didecylphthalonitrile (2.2g, 7.65mmol) and 4-pyridyl-3,6-dibutoxyphthalonitrile (0.3g, 0.85mmol) were refluxed in butan-1-ol (10ml). Lithium metal (0.12g, 17mmol) was added slowly in portions and refluxed was carried on for 12 hours in the dark. After cooling, glacial acetic acid (10ml) was added and the mixture stirred for 30 minutes. The solvents were removed under reduced pressure and methanol was added to the resulting green slurry. The solid was filtered and washed with methanol. The product was separated by column chromatography on silica (eluent: petroleum ether (bp. 40-60°C) to remove 1,4,8,11,15,18,22,25-octakis(decyl)phthalocyanine). The eluent was changed (petroleum ether (bp.40-60°C)-dichloromethane 9:1) and a second green fraction was collected. This was purified through a second silica column (eluents: petroleum ether (bp. 40-60°C) followed by petroleum ether (bp. 40-60°C)-dichloromethane 19:1). The product was recrystallised from THF/methanol to afford a green powder, 43mg (0.03mmol, 3.2%). [^{1}H NMR (300 MHz, benzene-d_6) δ 8.99 (d, 2H), 7.89-7.96 (m, 8H), 7.79 (s, 1H), 4.99 (t, 2H), 4.92 (t, 2H), 4.97 (qn, 8H), 4.49 (qn, 2H), 2.24-2.42 (m, 14H), 2.05 (qn, 2H), 0.99-1.89 (m, 93H), 0.65-0.86 (m, 21H), -0.48 (s, 2H) ppm. Found: C, 79.74; H, 9.88; N, 7.73%. $C_{105}H_{157}N_9O_2$ requires: C, 79.95; H, 10.03; N, 7.99%. λ_{max} (THF): Abs. 723 (ε=1.4x10^4) nm. MALDI-MS: isotopic cluster at 1577 [M^+]].

Preparation of 1,4-dibutoxy-2-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine:

An excess of lithium metal (0.1 g) was added to a rapidly stirring solution of 3,6-dibutoxy-4-(4-pyridyl)phthalonitrile (220 mg, 0.63 mmol) and 3,6-dihexylphthalonitrile (748 mg, 2.53 mmol) in 1-butanol (25 ml) at 120°C under nitrogen. Heating and stirring were continued for 12 hours in the absence of light. After cooling to room temperature, acetic acid (30 ml) was added and the resulting mixture was stirred for a further 20 minutes. The solvents were removed under reduced pressure and the resulting green slurry residue was washed with methanol. The resulting crude product was purified by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C)) to isolate the first fraction which contained symmetrical 1,4,8,11,15,18,22,25-octakis(hexyl)phthalocyanine (21% yield). The eluent was changed to petroleum ether (b.p. 40-60°C)/dichloromethane

(3:2) to collect the second fraction which was further purified by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C), then petroleum ether (b.p. 40-60°C)/dichloromethane 3:2). The resulting green solid was recrystallised from THF/acetone to afford *1,4-dibutoxy-2-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine* as green crystals (60 mg, 7.6%) [mp. 186°C. Found: C, 78.37; H, 8.80; N, 9.98%. $C_{82}H_{109}N_9O_2$ requires: C, 78.41; H, 8.85; N, 10.16%. MALDI-MS: isotopic cluster at 1240 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, 2H, J 5.9), 7.95 (m, 6H), 7.82 (s, 2H), 7.5 (s, 1H), 4.71 (t, 4H, J 6.3), 4.63 (m, 2H), 4.46 (m, 8H), 4.32 (t, 2H, J 7.1), 2.34 (quintet, 2H, J 7.2), 1.98-2.17 (m, 12H), 1.05-1.50 (m, 52H), 0.79-0.91 (m, 12H), 0.73 (t, 3H, J 7.3), 0.64 (t, 3H, J 7.2), 0.01 (s, 2H) ppm. λ_{max} (THF) 717 nm].

Preparation of 1,4-dibutoxy-2-thienyl-8,11,15,18,22,25-hexakis(decyl)phthalocyanine:

4-Thienyl-3,6-dibutoxyphthalonitrile (0.37g, 1.06mmol) and 3,6-didecylphthalonitrile (3.9g, 9.55mmol) were dissolved in butan-1-ol (15ml) and the mixture brought to reflux. Lithium metal (0.4g, 57mmol) was added slowly in portions. Reflux was carried on for 12 hours and the mixture was left to cool. Glacial acetic acid (10ml) was added and the mixture stirred for 30 minutes. The solvents were removed under reduced pressure and the residue was washed with methanol (3x100ml). The product was separated by column chromatography on silica (eluent: petroleum ether (bp. 40-60°C) to remove 1,4,8,11,15,18,22,25-octakis(decyl)phthalocyanine). The eluent was changed to dichloromethane/petroleum ether (bp. 40-60°C), increasing progressively the amount of dichloromethane from 5 to 25%. The second fraction collected was further purified by column chromatography on silica (same solvent systems used as previously described). A third purification by column chromatography was deemed necessary (eluent: 25% dichloromethane in petroleum ether (bp. 40-60°C)) to obtain a pure product which was recrystallised from THF/methanol as a green powder, 32mg (20μmol, 1.9%). [^{1}H NMR (300 MHz, C_6D_6) δ 8.29 (dd, 1H), 7.91 (q, 1H), 7.88 (s, 1H), 7.82 (s, 4H), 7.69 (s, 2H), 7.27 (dd, 1H), 4.98 (t, 2H), 4.85 (t, 2H), 4.78 (t, 2H), 4.46-4.64 (m, 10H), 2.07-2.4 (m, 16H), 1.6-1.83 (m, 12H), 0.97-1.58 (m, 79H), 0.68-0.96 (m, 21H), -0.35 (s, 2H) ppm. Found: C, 79.18; H, 9.87; N, 6.86%. $C_{104}H_{156}N_8O_2S$ requires: C, 78.94; H, 9.94; N, 7.08%. MALDI-MS: isotopic cluster at 1582 [M^+]. λ_{max} (THF): Abs. 727 (ε=1.85x10^4) nm].

Preparation of 1,4-dibutoxy-2-phenyl-8,11,15,18,22,25-hexakis(decyl)phthalocyanine:

4-Phenyl-3,6-dibutoxyphthalonitrile (0.37g, 1.06mmol) and 3,6-didecyl-phthalonitrile (3.9g, 9.55mmol) were dissolved in butan-1-ol (15ml) and the mixture brought to reflux. Lithium metal (0.4g, 57mmol) was added slowly in portions. Reflux was carried on for 12 hours and the mixture was left to cool. Glacial acetic acid (10ml) was added and the mixture stirred for 30 minutes. The solvents were removed under reduced pressure and the residue was washed with methanol (3x100ml). The product was separated by column chromatography on silica (eluent: petroleum ether (bp. 40-60°C) to remove 1,4,8,11,15,18,22,25-octakis(decyl)phthalocyanine). The eluent was changed to dichloromethane/petroleum ether (bp. 40-60°C), increasing progressively the amount of dichloromethane from 5 to 25%. The second fraction collected was further purified by column chromatography on silica (same solvent systems used as previously described). A third purification by column chromatography was deemed necessary (eluent: 25% dichloromethane in petroleum ether (bp. 40-60°C)) to obtain a pure product which was recrystallised from THF/methanol as a green powder, 22mg (14μmol, 1.3%). [^{1}H NMR (300 MHz, C_6D_6) δ 8.18 (d, 2H), 7.89-8.0 (m, 3H), 7.83 (s, 2H), 7.62 (s, 1H), 7.55 (t, 2H), 7.3-7.41 (m, 2H), 4.92-5.09 (m, 4H), 4.63-4.81 (m, 8H), 4.48 (t, 4H), 1.95-2.48 (m, 18H), 1.55-1.94 (m, 16H), 0.15-1.54 (m, 94H), -0.27 (s, 2H) ppm].

Preparation of 1,4-dibutoxy-2,3-diphenyl-8,11,15,18,22,25-hexakis(decyl)phthalocyanine:

4,5-Diphenyl-3,6-dibutoxyphthalonitrile (0.2g, 0.47mmol) and 3,6-didecyl-phthalonitrile (0.7g, 1.88mmol) were brought to reflux in butan-1-ol (10ml). Lithium metal (0.12g, 17mmol) was added slowly in portions and reflux was continued for 12 hours in the dark. The reaction mixture was allowed to cool and glacial acetic acid (10ml) was added and the solution stirred for 30 minutes. The solvents were removed under reduced pressure and the residue was chromatographed on silica (eluent: petroleum ether (bp. 40-60°C) to remove 1,4,8,11,15,18,22,25-octakis(decyl)phthalocyanine). The eluent was changed to dichloromethane/petroleum ether (bp. 40-60°C) 1:19. The isolated product was recrystallised from THF/methanol as a green powder, 50mg (0.03mmol, 6.5%). [^{1}H NMR (300 MHz, C_6D_6) δ 7.96 (s, 4H), 7.88 (s, 2H), 7.72 (d, 4H), 7.3 (t, 4H), 4.96 (t, 4H), 4.76 (t, 8H), 4.48 (t, 4H), 2.4 (m, 10H), 2.09 (qn, 4H), 1.69-1.87 (m, 12H), 1.57-1.67 (m, 4H), 1.4-1.57 (m, 12H), 0.89-1.39 (m, 74H), 0.74-0.87 (m, 14H), -0.17 (s, 2H) ppm. Found: C, 81.58; H, 9.94; N, 6.34%. $C_{112}H_{162}N_8O_2$ requires: C, 81.4; H, 9.88; N, 6.78%. λ_{max} (THF): Abs. 725 (ε=9.19x10^4), 711 (ε=9.12x10^4) nm. MALDI-MS: isotopic cluster at 1652 [M^+]].

Preparation of 1,4-dibutoxy-2-(*p*-hydroxymethylphenyl)-8,11,15,18,22,25-hexakis(decyl)-phthalocyanine:

To a rapidly stirring solution of 3,6-didecylphthalonitrile (1.01 g, 2.4 mmol) and 4-(*p*-hydroxymethylphenyl)-3,6-dibutoxyphthalonitrile (0.233 g, 0.6 mmol) in butan-1-ol (25 ml) at 120°C under nitrogen was added an excess of lithium metal (0.1 g, 14mmol). Heating and stirring were continued for 12 hours. After cooling to room temperature, glacial acetic acid (30 ml) was added and the resulting mixture was stirred for 20 minutes. This was poured onto methanol (100ml) and stirred for 5 minutes. The resulting precipitate was collected by filtration and air dried for 10 minutes. The green product was separated by column chromatography on silica (eluent: toluene). The first fraction contained symmetrical 1,4,8,11,15,18,22,25-octakis(decyl)phthalocyanine. The second fraction, which contained the required product, was collected and was precipitated from toluene by addition of methanol to afford *1,4-dibutoxy-2-(p-hydroxymethylphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine* as a dark green solid, 100 mg (0.062mmol, 10%). [^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, 2H, J= 8.1Hz), 7.94 (d, 4H, J=8.7Hz), 7.80 (s, 2H), 7.63 (d, 2H, J= 8.3Hz), 7.59 (s, 1H), 4.9 (d, 2H, J= 5.6Hz), 4.61-4.72 (m, 6H), 4.40-4.47 (m, 8H), 4.25 (t, 2H, J= 7.1Hz), 2.31 (qn, 2H, J=6.6Hz), 0.71-2.17 (m, 126H), 0.61 (t, 3H, J= 7.4Hz) ppm. Found: C, 80.00; H, 10.03; N, 6.86%. $C_{107}H_{160}N_8O_3$ requires: C, 80.00; H, 10.04; N; 6.98%; MALDI-MS: isotopic cluster at 1606 [M^+]. λ_{max} (THF): Abs. 728, 718 nm].

Preparation of 1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)-phthalocyanine:

The procedure for the synthesis of 1,4-dibutoxy-2-(p-hydroxymethylphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine above was followed using 4-(m-methoxyphenyl)-3,6-dibutoxyphthalonitrile (400 mg, 1.06 mmol) and 3,6-dihexylphthalonitrile (1.23 g, 4.24 mmol) in 1-butanol (25 ml). The resulting green crude product was purified by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C)/dichloromethane 7:3). The first fraction contained symmetrical 1,4,8,11,15,18,22,25-octakis(hexyl)phthalocyanine. The second green fraction contained *1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine* which was obtained as a green solid after recrystallisation from THF/MeOH (140 mg, 10%) [mp. 132-133°C. Found:

C, 78.78; H, 8.93; N, 8.64%. $C_{83}H_{112}N_8O_3$ requires: C, 78.51; H, 8.89; N, 8.82%. MALDI-MS: isotopic cluster at 1270 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (m, 4H), 7.84 (s, 2H), 7.60 (s, 1H), 7.55-7.57 (m, 3H), 7.07 (dd, 1H, J 7.5 and 1.6), 4.61-4.72 (m, 4H), 4.44-4.50 (m, 10H), 4.24 (t, 2H, J 7.26), 4.00 (s, 3H), 2.33 (quintet, 2H, J 7.2), 1.98-2.17 (m, 12H), 0.79-1.82 (m, 60H), 0.73 (t, 3H, J 7.3), 0.64 (t, 3H, J 7.3), 0.03 (s, 2H) ppm. λ_{max} (THF) 717 nm].

Preparation of 1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)-phthalocyanine:

To a refluxing solution of 3,6-dibutoxy-4-(m-methoxyphenyl)phthalonitrile (300 mg, 0.79 mmol) and 3,6-didecylphthalonitrile (1.295 g, 3.17 mmol) in 1-butanol (25 ml), was added an excess of lithium metal (0.1 g) under nitrogen with stirring. Heating and stirring were continued for 12 hours. After cooling to room temperature, acetic acid (30 ml) was added and the resulting mixture was stirred for 20 minutes. The resulting mixture was poured into methanol (100 ml) and stirred for 5 minutes. The resultant precipitate was collected and dried in air for 10 minutes. The green crude product was then purified by column chromatography (silica gel, eluent: petrol/DCM 7:3). The first fraction contained symmetrical 1,4,8,11,15,18,22,25-octakis (decyl) phthalocyanine. The second green fraction contained 1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)-phthalocyanine which was obtained as a green solid after recrystallisation from THF/MeOH (180 mg, 14%) [Found: C, 80.26; H, 10.14; N, 6.58%; $C_{107}H_{160}N_8O_3$ requires: C, 80.00; H, 10.04; N, 6.98%. MALDI-MS: isotopic cluster at 1606 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-8.01 (2H, m), 7.93 (2H, s), 7.78 (2H, s), 7.60-7.69 (4H, m), 7.15-7.19 (1H, m), 4.73-4.80 (6H, m), 4.34-4.52 (10H, m), 4.10 (3H, s), 2.31 (2H, quint, J 7.2), 0.80-2.46(123H, m), 0.75 (3H, t, J 7.6) ppm. λ_{max} (THF) 717nm].

Phthalocyanine derivatives prepared by condensation of 3,6-dibutoxy-4,5-di(m-methoxyphenyl)phthalonitrile and 3,6-didecylphthalonitrile:

The procedure for the synthesis of 1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine was followed using 3,6-dibutoxy-4,5-di(m-methoxyphenyl)phthalonitrile (400 mg, 0.826 mmol) and 3,6-didecylphthalonitrile (1.340 g, 3.28 mmol). According to the TLC analysis of the crude product (eluent:

toluene), there were four separable green spots. Thus it was purified using column chromatography (silica gel, eluent: toluene).

The first fraction contained a mixture of symmetrical 1,4,8,11,15,18,22,25-octakis(decyl)phthalocyanine and the expected asymmetrical 3:1 phthalocyanine. Further purification was done for the first fraction by column chromatography (silica gel, eluent: petrol/DCM 7:3). The second green fraction contained 1,4-dibutoxy-2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine (170 mg, 12%) [Found: C, 80.16; H, 9.69; N, 6.20%; $C_{114}H_{166}N_8O_4$ requires: C, 79.95; H, 9.77; N, 6.54%. MALDI-MS: isotopic cluster at 1712 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.98 (4H, m), 7.75 (2H, s), 7.27 (2H, d, J 7.9), 7.12 (2H, d, J 7.3), 7.00 (2H, br s), 6.85 (2H, dd, J 8.2 and 2.6), 4.64 (4H, m), 4.45 (4H, t, J 7.3), 4.38 (4H, t, J 7.3), 4.30 (4H, t, J 6.6), 3.76 (6H, s), 0.89-2.17 (112H, m), 0.80 (12H, t, J 6.9), 0.66(6H, t, J 7.4) ppm. λ_{max} (THF) 709nm].

The second fraction contained an isomeric mixture of 2:2 phthalocyanine derivatives adjacent and opposite. Separation and purification was obtained by column chromatography (silica gel, eluent: petrol/DCM 1:1). The first green fraction contained 1,4,15,18-tetrabutoxy-2,3,16,17-tetra-(m-methoxyphenyl)-8,11,22,25-tetrakis(decyl)-phthalocyanine which was recrystallised from THF/acetone to afford the product (20 mg, 1.2 %) as green crystals [Found: C, 77.78; H, 8.58; N, 6.09%; $C_{116}H_{154}N_8O_8$ requires: C, 77.90; H, 8.68; N, 6.27%. MALDI-MS: isotopic cluster at 1788 [M^+]. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.01 (4H, s), 7.24 (4H, d, 7.9), 7.10 (4H, d, 7.9), 6.99 (4H, s), 6.83 (4H, dd, 8.2 and 2.6), 4.64 (8H, m), 4.27 (8H, m), 3.74 (12H, s), 2.10 (8H, quint, J 6.3), 1.80 (8H, quint, J 6.2), 1.19-1.61 (56H, m), 0.96 (8H, quint, J 7.5), 0.79 (12H, t, J 6.9), 0.63 (12H, t, J 7.2) ppm. λ_{max} (THF) 728nm].

The second green fraction contained 1,4,8,11-tetrabutoxy-2,3,9,10-tetra-(m-methoxyphenyl)-15,18,22,25-tetrakis(decyl)phthalocyanine which was obtained (80 mg, 5%) as a green waxy solid [Found: C, 77.96; H, 8.65; N, 6.03%; $C_{116}H_{154}N_8O_8$ requires: C, 77.90; H, 8.68; N, 6.27%. MALDI-MS: isotopic cluster at 1788 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-8.03 (4H, m), 6.82-7.89 (16H, m), 4.77 (4H, m), 4.63 (4H, m), 4.48 (4H, t, J 7.1), 4.27-4.30 (4H, m), 3.75 (12H, s), 0.74-2.21 (98H, m), 0.65 (6H, t, J 7.3) ppm. λ_{max} (THF) 718 and 746nm].

The third fraction contained another asymmetrical phthalocyanine 1:3. Further purification was obtained using column chromatography (silica gel, eluent: toluene/ethyl acetate 30:1) to afford 1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-

methoxyphenyl)-22,25-di(decyl)phthalocyanine (90 mg, 6%) as a green waxy solid [Found: C, 75.69; H, 7.98; N, 5.53%; $C_{118}H_{142}N_8O_{12}$ requires: C, 76.02; H, 7.68; N, 6.01%. MALDI-MS: isotopic cluster at 1864 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (2H, s), 6.81-7.28 (24H, m), 4.75 (8H, m, 4×Ar-OCH_2~), 4.64 (4H, m, 2×Ar-OCH_2~), 4.30 (4H, t, J 6.9, Ar-CH_2~), 3.75 (6H, s, 2×Ar-OCH_3), 3.75 (12H, s, 4×Ar-OCH_3), 0.74-2.17 (74H, m), 0.66 (6H, t, J 7.4), 0.08 (2H, s, 2×~NH) ppm. λ_{max} (1.07×10^{-5} M in THF) 742nm (ε= 1.69×10^5)].

The fourth fraction was collected by changing the eluent (toluene/THF 20:1) and it was assigned to the symmetrical phthalocyanine which was further purified by column chromatography (silica gel, eluent: petroleum ether/THF 10:1) to afford 1,4,8,11,15,18,22,25-octabutoxy-2,3,9,10,16,17,23,24-octa-(m-methoxyphenyl)-phthalocyanine (40 mg, 2.5%) and obtained as a waxy green solid [MALDI-MS: isotopic cluster at 1940 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (8H, dd, J 7.5 and 8.2), 7.05 (8H, d, J 7.5), 7.00 (8H, s), 6.81 (8H, dd, J 8.2 and 2.3), 4.73 (16H, t, J 5.9), 1.71 (16H, quint, J 6.6), 1.10 (16H, quint, J 7.5), 0.74 (24H, t, J 7.5) ppm. λ_{max} (THF) 748 and 768nm].

Phthalocyanine derivatives prepared by condensation of 4,5-di(m-methoxyphenyl)-3,6-dibutoxyphthalonitrile and 3,6-dihexylphthalonitrile:

The procedure for the synthesis of 1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine above was followed using 4,5-di(m-methoxyphenyl)-3,6-dibutoxyphthalonitrile (400 mg, 0.826 mmol) and 3,6-dihexylphthalonitrile (977 mg, 3.30 mmol). According to the TLC analysis of the crude product (eluent: toluene), there were four separable green spots. The crude product was purified using column chromatography (silica gel, eluent: toluene) obtaining four main fractions.

The first fraction contained a mixture of symmetrical 1,4,8,11,15,18,22,25-octakis(hexyl)phthalocyanine and the expected asymmetrical 3:1 phthalocyanine. Further purification of the first fraction was achieved by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C)/dichloromethane 7:3) and 1,4,8,11,15,18,22,25-octakis(hexyl)phthalocyanine was collected as the first green fraction. The following second green fraction was collected and it was found to contain *1,4-dibutoxy-2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine* (150 mg, 13%) [mp. 211-212°C. Found: C, 78.76; H, 8.58; N, 8.01%. $C_{90}H_{118}N_8O_4$ requires: C, 78.56; H, 8.64; N,

8.14%. MALDI-MS: isotopic cluster at 1376 [M^+]. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.96 (s, 4H), 7.83 (s, 2H), 7.27 (d, 2H, J 7.9), 7.10 (d, 2H, J 6.9), 7.00 (m, 2H), 6.84 (dd, 2H, J 7.9 and 2.6), 4.64 (m, 4H), 4.43-4.52 (m, 8H), 4.28 (t, 4H, J 6.6), 3.75 (s, 6H), 2.01-2.17 (m, 12H), 0.85-1.81 (m, 50H), 0.81 (t, 12H, J 6.9), 0.64 (t, 6H, J 7.3), 0.01 (s, 2H) ppm. λ_{max} (THF) 726 and 711 nm].

The second fraction was collected and further purified by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C)/dichloromethane 1:1) to isolate the second green fraction containing *1,4,8,11-tetrabutoxy-2,3,9,10-tetra-(m-methoxyphenyl)-15,18,22,25-tetrakis(hexyl)phthalocyanine* as a green solid product (90 mg, 7%) [mp. 268-270°C. Found: C, 76.96; H, 7.98; N, 6.89%. $C_{100}H_{122}N_8O_8$ requires: C, 76.79; H, 7.86; N, 7.16%. MALDI-MS: isotopic cluster at 1564 [M^+]. ^{1}H NMR (270MHz, $CDCl_3$) δ 7.91 (s, 4H), 6.99-7.22 (m, 12H), 6.84 (m, 4H), 4.77 (m, 4H), 4.62 (m, 4H), 4.47 (t, 4H, J 7.6), 4.25 (t, 4H, J 7.6), 3.64 (s, 12H), 2.17 (quintet, 4H, J 7.3), 2.03 (quintet, 4H, J 7.6), 0.81-1.84 (m, 52H), 0.74 (t, 6H, J 7.3), 0.64 (t, 6H, J 7.3), 0.2 (s, 2H) ppm. λ_{max} (THF) 717 and 745 nm].

The third fraction contained another unsymmetrical phthalocyanine 1:3. Further purification was achieved by column chromatography (silica gel, eluent: n-hexane/THF 4:1) to afford *1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-methoxyphenyl)-22,25-di(hexyl)phthalocyanine* as a green solid (60 mg, 4%) [mp. 210-211°C. Found: C, 74.59; H, 7.28; N, 5.98%. $C_{110}H_{126}N_8O_{12}$ requires: C, 75.40; H, 7.25; N, 6.39%. MALDI-MS: isotopic cluster at 1752 [M^+]. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.98 (s, 2H), 6.99-7.24 (m, 18H), 6.80-6.87 (m, 6H), 4.60-4.73 (m, 12H), 4.29 (t, 4H, J 6.9), 3.74 (s, 6H), 3.73 (s, 12H), 2.09 (m, 4H), 0.92-1.83 (m, 36H), 0.89 (t, 6H, J 6.9), 0.75 (t, 12H, J 7.3), 0.65 (t, 6H, J 7.3), 0.07 (s, 2H) ppm. λ_{max} (THF) 742 nm].

Phthalocyanine derivatives prepared by condensation of 3,6-dibutoxy-4,5-di(4-pyridyl)-phthalonitrile and 3,6-dihexylphthalonitrile:

An excess of lithium metal (0.1 g) was added to a rapidly stirring solution of 3,6-dibutoxy-4,5-di(4-pyridyl)phthalonitrile (150 mg, 0.352 mmol) and 3,6-dihexylphthalonitrile (416 mg, 1.41 mmol) in 1-butanol (25 ml) at 120°C under nitrogen. Heating and stirring were continued for 12 hours in the absence of light. After cooling to room temperature, acetic acid (30 ml) was added and the resulting mixture was stirred for a further 20 minutes. The resulting mixture was poured onto methanol (100 ml) and stirred for 5 minutes. The

resulting precipitate was collected and dried in air for 10 minutes. TLC analyses were checked for both the precipitate and the filtrate.

According to the TLC analysis of the precipitate (eluent petroleum ether (b.p. 40-60°C)/THF 9:1), there were three separable green spots. Thus the precipitate was purified by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C)/THF 9:1). The first fraction contained symmetrical 1,4,8,11,15,18,22,25-octakis(hexyl)phthalocyanine (23% yield). The eluent was changed to petroleum ether (b.p. 40-60°C)/THF (3:2) to collect the second fraction containing *1,4-dibutoxy-2,3-di-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine* which was recrystallised from THF/MeOH to yield green crystals (40 mg, 10%) [mp. 256°C. Found: C, 78.38; H, 8.57; N, 10.63%. $C_{86}H_{112}N_{10}O_2$ requires: C, 78.52; H, 8.65; N, 10.44%. MALDI-MS: isotopic cluster at 1318 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, 4H, J 6), 8.02 (s, 4H), 7.84 (s, 2H), 7.40 (d, 4H, J 6.1), 4.62 (t, 4H, J 7.7), 4.52 (t, 4H, J 7.6), 4.46 (t, 4H, J 7.3), 4.36 (t, 4H, J 6.6), 2.11 (quintet, 12H, J 7.6), 1.80 (quintet, 4H, J 6.6), 1.26-1.55 (m, 40H), 0.80-1.02 (m, 18H), 0.66 (t, 6H, J 7.2), 0.07 (s, 2H) ppm. λ_{max} (THF) 719 nm]. The eluent was then changed to petroleum ether (b.p. 40-60°C)/THF (2:3) to collect the third fraction. The solvent was evaporated to leave a green solid which was recrystallised from THF/MeOH to afford *1,4,8,11-tetrabutoxy-2,3,9,10-tetra-(4-pyridyl)-15,18,22,25-tetrakis-(hexyl)phthalocyanine* as a green solid product (20 mg, 4%) [mp. 256°C. MALDI-MS: isotopic cluster at 1448 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (dd, 8H, J 6 and 1.2), 7.96 (s, 4H), 7.38 (dd, 8H, J 6 and 1.5), 4.80 (t, 4H, J 6.9), 4.57 (t, 4H, J 7), 4.46 (t, 4H, J 7.7), 4.33 (t, 4H, J 6.9), 2.16 (m, 4H), 2.03 (m, 4H),1.86 (m, 8H), 1.25-1.69 (m, 28H), 1.13 (quintet, 4H, J 7.2), 0.78-0.98 (m, 18H), 0.64 (t, 6H, J 7.3), 0.23 (s, 2H) ppm. λ_{max} (THF) 716 and 742 nm].

The TLC analysis of the filtrate (eluent: toluene/THF 4:1) indicated that there were also three separable green spots. Thus the solvents were removed under reduced pressure and the resulting green slurry crude product was purified by column chromatography (silica gel, eluent: toluene/THF 3:1). The first green fraction contained a very low yield of the previous isolated compound. The second fraction was collected after changing the eluent to toluene/THF (2:1) then (1:1). The second fraction contained another unsymmetrical phthalocyanine 1:3. Further purification was achieved by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C)/THF 1:4) to afford *1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(4-pyridyl)-22,25-di(hexyl)phthalocyanine* (23 mg, 4%) [MALDI-MS: isotopic cluster at 1578 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (m, 12H), 8.03 (s, 2H),

7.33-7.40 (m, 12H), 4.79 (t, 4H, J 6.8), 4.72 (t, 4H, J 6.6), 4.60 (t, 4H, J 7.7), 4.35 (t, 4H, J 6.9), 2.1 (m, 4H), 1.84 (m, 4H), 1.03-1.74 (m, 38H), 0.94 (t, 6H, J 7), 0.77-0.90 (m, 6H), 0.64 (t, 6H, J 7.3), 0.33 (s, 2H) ppm. λ_{max} (THF) 739 nm].

General procedure for insertion of zinc metal in the above metal-free phthalocyanine derivatives:

To a refluxing and stirring solution of the required metal-free phthalocyanine in butan-1-ol, was added zinc acetate dihydrate 99.999% (excess). The reaction mixture was refluxed until reaction was complete (as shown by TLC). The solvent was removed under reduced pressure and the product was purified by column chromatography using appropriate eluent systems.

Preparation of [1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)-phthalocyaninato]zinc[II] (compound number **11**):

From the reaction of 1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine (160 mg, 0.99 mmol), the resulting blue product was purified by column chromatography (silica gel, eluent: DCM) to afford [1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyaninato]zinc[II] as a blue solid (158 mg, 95%) [m.p. 91-92.2°C. Found: C, 77.16; H, 9.68; N, 6.50%; $C_{107}H_{158}N_8O_3Zn$ requires: C, 76.96; H, 9.54; N, 6.71%. MALDI-MS: isotopic cluster at 1669 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (1H, d, J 7.5), 7.75 (1H, d, J 7.7), 7.66 (2H, m), 7.60 (1H, d, J 8.00), 7.57 (1H, s), 7.21-7.29 (2H, m), 7.11-7.14 (1H, m), 7.01 (2H, m), 4.75 (2H, t, J 7.5), 4.61 (2H, t, J 7.5), 4.46 (2H, t, J 7.0), 4.21 (2H, t, J 6.5), 4.06-4.09 (5H, m), 3.82-3.84 (4H, m), 3.68 (2H, br s), 0.69-2.30 (128H, m) ppm. λ_{max} (2.3×10^{-6} M in THF) 715nm ($\varepsilon = 3.17\times10^5$)].

Preparation of [1,4-dibutoxy-2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)-phthalocyaninato]zinc[II] (compound number **14**):

The above procedure was followed using 2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine (80 mg, 0.046 mmol) and zinc acetate dihydrate (30 mg, excess). The resulting blue product was purified by column chromatography (silica gel, eluent: toluene) to afford [1,4-dibutoxy-2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyaninato]zinc[II] as a blue waxy

product (77 mg, 93%) [Found: C, 77.44; H, 9.40; N, 5.93%; $C_{114}H_{164}N_8O_4Zn$ requires: C, 77.10; H, 9.31; N, 6.31%. MALDI-MS: isotopic cluster at 1775 [M^+]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (2H, d, J 7.6), 7.74 (2H, d, J 7.7), 7.31 (2H, m), 7.24 (2H, s), 7.08 (2H, s), 6.90 (2H, dd, J 2.4 and 8.1), 6.75 (2H, s), 4.71 (4H, m), 4.45 (4H, m), 4.10 (4H, m), 3.79 (6H, s), 3.60 (4H, m), 0.69-2.30 (122H, m), 0.70 (6H, t, J 7.4) ppm. λ_{max} (2.25×10^{-6} M in THF) 712nm ($\varepsilon = 2.76 \times 10^5$)].

Preparation of [1,4,15,18-tetrabutoxy-2,3,16,17-tetra-(m-methoxyphenyl)-8,11,22,25-tetrakis(decyl)phthalocyaninato]zinc[II] (compound number **20**):

The above procedure was followed using 1,4,15,18-tetrabutoxy-2,3,16,17-tetra-(m-methoxyphenyl)-8,11,22,25-tetrakis(decyl)phthalocyanine (15 mg, 0.008 mmol) and zinc acetate dihydrate (10 mg, excess). The resulting blue product was purified by column chromatography (silica gel, eluent: petroleum ether/THF 10:1) to afford [1,4,15,18-tetrabutoxy-2,3,16,17-tetra-(m-methoxyphenyl)-8,11,22,25-tetrakis(decyl)-phthalocyaninato]zinc[II] as a blue waxy product (15 mg, 90%) [MALDI-MS: isotopic cluster at 1851 [M^+]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (4H, s), 7.23-7.29 (4H, m), 7.14 (4H, d, J 6.9), 7.03 (4H, s), 6.85 (4H, dd, J 2.6 and 8.0), 4.66 (8H, m), 4.34 (8H, m), 3.75 (12H, s), 2.10-2.15 (8H, m), 1.84 (8H, quint, J 7.3), 1.21-1.62 (60H, m), 1.02 (8H, quint, J 7.5), 0.78-0.87 (12H, m), 0.65 (12H, t, J 7.4) ppm. λ_{max} (1.69×10^{-5} M in THF) 732nm ($\varepsilon = 1.11 \times 10^5$) and 703nm].

Preparation of [1,4,8,11-tetrabutoxy-2,3,9,10-tetra-(m-methoxyphenyl)-15,18,22,25-tetrakis(decyl)phthalocyaninato]zinc[II] (compound number **17**):

The above procedure was followed using 1,4,8,11-tetrabutoxy-2,3,9,10-tetra-(m-methoxyphenyl)-15,18,22,25-tetrakis(decyl)phthalocyanine (70 mg, 0.039 mmol) and zinc acetate dihydrate (30 mg, excess). The purification of the resulting blue product was achieved by column chromatography (silica gel, eluent: petrol/THF 9:1) to afford [1,4,8,11-tetrabutoxy-2,3,9,10-tetra-(m-methoxyphenyl)-15,18,22,25-tetrakis(decyl)-phthalocyaninato]zinc[II] as a blue waxy solid (66 mg, 91%) [Found: C, 75.55; H, 8.55; N, 5.40%; $C_{116}H_{152}N_8O_8Zn$ requires: C, 75.23; H, 8.27; N, 6.05%. MALDI-MS: isotopic cluster at 1851 [M^+]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (4H, s), 6.98-7.28 (12H, m), 6.80-6.86 (4H, m), 4.83 (4H, m), 4.67 (4H, m), 4.49 (4H, t, J 7.4), 4.32 (4H, m), 3.74 (12H,

s), 0.74-2.23 (98H, m), 0.64 (6H, t, J 7.4) ppm. λ_{max} (2.2×10^{-6} M in THF) 719nm ($\varepsilon=3.27\times10^{5}$)].

Preparation of [1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-methoxyphenyl)-22,25-di(decyl)phthalocyaninato]zinc[II] (compound number **23**):

The above procedure was followed using 1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-methoxyphenyl)-22,25-di(decyl)phthalocyanine (70 mg, 0.037 mmol) and zinc acetate dihydrate (30 mg, excess). The purification of the resulting greenish blue product was achieved by column chromatography (silica gel, eluent: petrol/THF 9:2) to afford [1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-methoxyphenyl)-22,25-di(decyl)phthalocyaninato]zinc[II] as a greenish blue solid (65 mg, 90% [Found: C, 73.29; H, 7.85; N, 5.40%; $C_{118}H_{140}N_8O_{12}Zn$ requires: C, 73.52; H, 7.32; N, 5.81%. MALDI-MS: isotopic cluster at 1928 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (2H, s), 7.04-7.29 (18H, m), 6.81-6.87 (6H, m), 4.82 (8H, m), 4.67 (4H, m), 4.49 (4H, t, J 7.3), 3.75 (6H, s), 3.74 (6H, s), 3.73 (6H, s), 0.74-2.14 (74H, m), 0.66 (6H, t, J 7.6) ppm. λ_{max} (0.104×10^{-6} M in THF) 732nm ($\varepsilon=1.75\times10^{5}$)].

Preparation of [1,4,8,11,15,18,22,25-octabutoxy-2,3,9,10,16,17,23,24-octa-(m-methoxyphenyl)phthalocyaninato]zinc[II] (compound number **26**):

The above procedure was followed using 1,4,8,11,15,18,22,25-octabutoxy-2,3,9,10,16,17,23,24-octa-(m-methoxyphenyl)phthalocyanine (40 mg, 0.21 mmol) and zinc acetate dihydrate (20 mg, excess). The resulting green product was purified by column chromatography (silica gel, eluent: petrol/THF 7:3) to afford [1,4,8,11,15,18,22,25-octabutoxy-2,3,9,10,16,17,23,24-octa-(m-methoxyphenyl)phthalocyaninato]zinc[II] (40 mg, 2.5%) as a green solid [MALDI-MS: isotopic cluster at 2005 [M^+]. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.23 (8H, dd, J 7.5 and 7.9), 7.05 (8H, d, J 7.5), 7.02 (8H, s), 6.81 (8H, dd, J 7.9 and 2.3), 4.79 (16H, m), 3.72 (24H, s), 1.69 (16H, quint, J 6.9), 1.06 (16H, quint, J 6.3), 0.75 (24H, t, J 7.2) ppm; λ_{max} (1.9×10^{-6} M in THF) 742nm ($\varepsilon=3.41\times10^{5}$)].

Preparation of [1,4-dibutoxy-2-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)-phthalocyaninato]zinc (compound number **34**):

The above procedure was followed using 1,4-dibutoxy-2-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine (50 mg, 0.04 mmol) and zinc acetate

dihydrate (20 mg, excess). The resulting blue product was purified by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C)/THF 4:1) to afford *[1,4-dibutoxy-2-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyaninato]zinc* which was recrystallised from THF/MeOH to yield blue crystals (42 mg, 81%) [mp. 183-184°C. Found: C, 74.90; H, 8.35; N, 9.41%. $C_{81}H_{107}N_9O_2Zn$ requires: C, 74.60; H, 8.27; N, 9.67%. MALDI-MS: isotopic cluster at 1304 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, 2H, J 4.9), 7.96 (d, 2H, J 5.9), 7.90 (m, 6H), 7.65 (s, 1H), 4.81 (t, 4H, J 6.3), 4.73 (m, 2H), 4.60 (m, 8H), 4.43 (t, 2H, J 6.9), 2.37 (quintet, 2H, J 7.3), 2.04-2.26 (m, 12H), 0.97-1.91 (m, 52H), 0.79-0.91 (m, 12H), 0.72 (t, 3H, J 7.1), 0.61 (t, 3H, J 7.2) ppm. λ_{max} (3.06×10^{-6} M in THF) 718 ($\varepsilon=1.49\times10^5$) nm].

Preparation of [1,4-dibutoxy-2,3-di-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)-phthalocyaninato]zinc (compound number **38**):

The above procedure was followed using 1,4-dibutoxy-2,3-di-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine (40 mg, 0.03 mmol) and zinc acetate dihydrate (20 mg, excess). The resulting blue product was purified by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C)/THF 3:2) to afford *[1,4-dibutoxy-2,3-di-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyaninato]zinc* which was recrystallised from THF/MeOH to yield green crystals (35 mg, 85%) [mp. >290°C. Found: C, 74.46; H, 8.05; N, 10.04%. $C_{86}H_{110}N_{10}O_2Zn$ requires: C, 74.78; H, 8.03; N, 10.14%. MALDI-MS: isotopic cluster at 1381 [M^+]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, 4H, J 5.9), 7.92 (m, 6H), 7.40 (d, 4H, J 4.4), 4.70 (t, 4H, J 7.7), 4.60 (m, 8H), 4.41 (t, 4H, J 6.8), 2.17 (quintet, 12H, J 7.6), 1.86 (quintet, 4H, J 6.7), 1.18-1.71 (m, 40H), 0.93 (t, 6H, J 7.1), 0.84 (t, 12H, J 6.9), 0.62 (t, 6H, J 7.3) ppm. λ_{max} (2.01×10^{-6} M in THF) 719 ($\varepsilon=1.44\times10^5$) nm].

Preparation of [1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)-phthalocyaninato]zinc(II) (compound number **28**):

The above procedure was followed using 1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine (40 mg, 0.031 mmol) and zinc acetate dihydrate (10 mg, excess). The resulting blue product was purified by column chromatography (silica gel, eluent: n-hexane/THF 10:1) to afford *[1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyaninato]zinc* as a blue solid (38

mg, 92%) [Found: C, 74.98; H, 8.41; N, 8.03%. $C_{83}H_{110}N_8O_3Zn$ requires: C, 74.77; H, 8.32; N, 8.40%. MALDI-MS: isotopic cluster at 1333 [M^+]. ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (m, 6H), 7.50-7.61 (m, 4H), 7.01 (m, 1H), 4.72-4.81 (m, 6H), 4.56-4.61 (m, 8H), 4.53 (t, 2H, J 6.9), 4.0 (s, 3H), 2.35 (quintet, 2H, J 7.4), 2.07-2.22 (m, 12H), 1.02-1.84 (m, 48H), 0.78-0.87 (m, 12H), 0.71 (t, 3H, J 7.3), 0.61 (t, 3H, J 7.3) ppm. λ_{max} (3×10^{-6} M in THF) 714 ($\varepsilon = 1.63\times10^5$) nm].

Preparation of [1,4-bis(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)-phthalocyaninato]zinc(II) (compound number **30**):

To a solution of 3,6-bis(3-methoxyphenyl)phthalonitrile (0.13 g, 0.38 mmol) and 3,6-didecylphthalonitrile (0.94 g, 2.29 mmol, 6 eq.) in refluxing pentan-1-ol (10 ml) was added DBU (0.3 g, 0.7 eq.). The solution was refluxed for 1 hour, then zinc acetate dihydrate (99.999%, 0.18 g, 0.3 eq.) was added. The solution turned green and reflux was continued for a further 24 hours. After cooling, methanol (10 ml) was added and the precipitate was filtered and washed with methanol (3x10 ml). The product was purified by column chromatography over silica (eluent: petroleum ether (bp. 40-60°C)/ dichloromethane 4:1) to remove [1,4,8,11,15,18,22,25-octakis(decyl)phthalocyaninato] zinc(II). Then the eluent was changed to petroleum ether (bp. 40-60°C)/dichloromethane (1:1) and *[1,4-bis(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyaninato] zinc(II)* was isolated as a green solid which was recrystallised from THF/acetone [MALDI-MS: isotopic cluster at 1632 [M^+]. λ_{max} (abs.) 710 (THF) nm. λ_{max} (em.) 722.4 (THF) nm. ^1H NMR (270 MHz, $CDCl_3$+1 drop pyridine-d_5) δ 7.88 (s, 2H), 7.77 (s, 2H), 7.68 (d, 2H), 7.48 (t, 4H, J 8), 7.3 (t, 2H, J 8), 7.07 (m, 2H), 6.63 (m, 2H), 4.42 (m, 8H), 3.83 (s, 6H), 2.98-3.16 (m, 2H), 2.12 (m, 8H), 0.71-1.6 (m, 106H) ppm].

Preparation of [1,4-dibutoxy-2-bromo-8,11,15,18,22,25-hexakis(decyl)phthalocyaninato] zinc(II) (compound number **32**):

3,6-Didecylphthalonitrile (1 g, 2.45 mmol), 4-bromo-3,6-dibutoxyphthalonitrile (0.3 g, 0.82 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.18 g, 8.82 mmol) and zinc acetate dihydrate (99.999%, 0.27 g, 1.23 mmol) were refluxed under nitrogen in dry butan-1-ol (20 ml) for 3 days in the dark. After cooling to room temperature, the solvent was removed under reduced pressure and the residue washed with methanol (3x50 ml). The crude material was separated by column chromatography over silica (eluent:

petroleum ether (bp. 40-60°C)/dichloromethane 4:1). The first fraction contained [1,4,8,11,15,18,22,25-octakis(decyl)phthalocyaninato]zinc(II) (240 mg, 5.8%). The eluent was then changed to petroleum ether (bp. 40-60°C)/dichloromethane (1:1) and a second fraction was collected. This fraction was further purified by preparative TLC on silica (eluent: petroleum ether (bp. 40-60°C)/dichloromethane 3:2). The second fraction was collected, the solvent evaporated and the residue recrystallised from THF/methanol to afford *[1,4-dibutoxy-2-bromo-8,11,15,18,22,25-hexakis(decyl)phthalocyaninato]zinc(II)* as a dark green solid (50 mg, 3.7%) [^{1}H NMR (300 MHz, C_6D_6) δ 7.85-8.0 (m, 7H), 5.08 (t, 2H), 4.96 (t, 4H), 4.79 (m, 8H), 4.35 (t, 2H), 1.1-2.5 (m, 104H), 0.84 (m, 24H) ppm. λ_{max} (abs.) 716.5 (THF) nm].

Preparation of substituted di(hydroxy/alkoxy)silicon phthalocyanines (I):

Preparation of [1,4,8,11,15,18,22,25-octakis(pentyl)phthalocyaninato]dihydroxysilicon (compound number **1**):

A mixture of metal-free 1,4,8,11,15,18,22,25-octakis(pentyl)phthalocyanine (400mg, 0.37mmol) and tri-n-butylamine (20ml) was refluxed in benzene (70ml) under nitrogen. The solution was dried by distilling off some of the solvent (15ml). The solution was left to cool to room temperature and trichlorosilane (1ml) was injected via a syringe directly into the solution. This was then stirred in the dark overnight. TLC analysis (eluent: petroleum ether (bp. 40-60°C)/THF 20:1) showed that a small amount of starting material was left. The mixture was then poured cautiously into water (100ml) and triethylamine (60ml) was added slowly. The white precipitate was removed by filtration and washed with toluene until the washings were almost clear. The organic phase was separated, washed with 20% aqueous HCl (5x100ml), brine and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent was removed under reduced pressure. The green residue was chromatographed over silica (eluent: petroleum ether (bp. 40-60°C)/THF 20:1). This afforded a blue-green fraction which *contained [1,4,8,11,15,18,22,25-octakis(pentyl)phthalocyaninato]dihydroxysilicon* (210mg, 0.18mmol, 48%) which appeared soluble in most organic solvents (acetone, petroleum ether, toluene and THF). [^{1}H NMR (270MHz, C_6D_6) δ 7.95 (s, 8H), 4.53 (t, 16H), 2.25 (quintet, 16H), 1.7 (quintet, 16H), 1.41 (m, 16H), 0.9 (t, 24H), -5.8 (br s, 2H) ppm. ^{13}C NMR (67.5MHz, C_6D_6) δ 149.0, 139.5, 134.5, 131.25, 33.1, 32.1, 30.8, 23.4, 14.4 ppm.

Found: C, 76.23; H, 8.77; N, 9.48%. $C_{72}H_{98}N_8O_2Si$ requires: C, 76.15; H, 8.69; N, 9.87%. λ_{max} (abs.) 703nm (THF), $\varepsilon = 2.8x10^5$. MALDI-MS: clusters at 1135 (60%) and 1118 (100%, M-H_2O). mp 194-5°C].

Preparation of [1,4,8,11,15,18,22,25-octakis(hexyl)phthalocyaninato]dihydroxysilicon (compound number **3**):

A mixture of metal-free 1,4,8,11,15,18,22,25-octakis(hexyl)phthalocyanine (170mg, 0.14mmol) and tri-n-butylamine (20ml) was refluxed in benzene (70ml) under nitrogen. The solution was dried by distilling off some of the solvent (15ml). The solution was left to cool to room temperature and trichlorosilane (1ml) was injected via a syringe directly into the solution. This was then stirred in the dark for 6 hours. More trichlorosilane (0.5ml) was added and the solution left to stir in the dark for 12 hours. TLC analysis (eluent: petroleum ether (bp. 40-60°C)) showed some starting material was left. More trichlorosilane (0.5ml) was added and the solution left to stir in the dark for another 12 hours. The mixture was then poured cautiously into water (100ml) and triethylamine (60ml) was added slowly. The white precipitate was removed by filtration and washed with toluene until the washings were almost clear. The organic phase was separated, washed with 20% aqueous HCl (5x100ml), brine and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent was removed under reduced pressure. The green residue was chromatographed over silica (eluent: petroleum ether (bp. 40-60°C)) to remove traces of starting material. The eluent was then changed to petroleum ether (bp. 40-60C)/THF 4:1. This afforded a blue-green fraction which contained *[1,4,8,11,15,18,22,25-octakis(hexyl)phthalocyaninato]dihydroxysilicon* (60mg, 48μmol, 34%) which appeared soluble in most organic solvents (acetone, methanol, ethanol, petroleum ether, toluene and THF). [^{1}H NMR (270MHz, C_6D_6) δ 7.97 (s, 8H), 4.53 (t, 16H), 2.17 (m, 16H), 1.61 (m, 16H), 1.19-1.42 (m, 32H), 0.84 (t, 24H), -5.4 (br s, 2H) ppm. Found: C, 76.94; H, 9.33; N, 8.43%. $C_{80}H_{114}N_8O_2Si$ requires: C, 76.99; H, 9.21; N, 8.98%. λ_{max} (abs.) 704nm (THF), $\varepsilon = 2.4x10^5$. λ_{max} (em.) 715nm (THF). MALDI-MS: clusters at 1247 (20%) and 1230 (100%, M-H_2O)].

Preparation of [1,4,8,11,15,18,22,25-octakis(octyl)phthalocyaninato]dihydroxysilicon (compound number **5**):

The above procedure was followed using metal-free 1,4,8,11,15,18,22,25-octakis(octyl)phthalocyanine (200 mg, 0.15 mmol), tri-n-butylamine (2 ml) and trichlorosilane (2 ml) in benzene (50 ml). The resulting green residue was chromatographed over silica (eluent: petroleum ether (bp. 40-60°C)) to remove traces of unreacted starting material. The eluent was then changed (petroleum ether (bp. 40-60°C)/THF 4:1). This afforded a blue-green fraction which contained *[1,4,8,11,15,18,22,25-octakis(octyl)phthalocyaninato]dihydroxysilicon* which appeared soluble in most organic solvents (acetone, petroleum ether, toluene and THF) (110 mg, 54%) [^{1}H NMR (270 MHz, C_6D_6) δ 7.89 (s, 8H), 4.45 (t, 16H), 2.08 (m, 16H), 1.52 (m, 16H), 1.0-2.0 (m, 64H), 0.74 (t, 24H), -5.41 (br s, 2H) ppm. λ_{max} ($\varepsilon x10^5$) 703.5 (2.3) nm in THF. MALDI-MS: isotopic clusters at 1472 [M^+, 60%] and 1455 [M^+-H_2O, 100%]. Found: C, 78.15; H, 10.03; N, 7.38%. $C_{96}H_{146}N_8O_2Si$ requires: C, 78.31; H, 9.99; N, 7.61%].

Preparation of 1,4,8,11,15,18,22,25-octakis(decyl)phthalocyaninatodihydroxysilicon (compound number 7):

The above procedure was followed using metal-free 1,4,8,11,15,18,22,25-octakis(decyl)phthalocyanine (200 mg, 0.12 mmol), tri-n-butylamine (2 ml) and trichlorosilane (1.5 ml) in benzene (50 ml). The resulting product was purified by column chromatography on silica (eluent: petroleum ether (bp. 40-60°C)/toluene 3:1) to remove unreacted starting material and some yellow and purple impurities. The solvent ratio was then changed to (2.5:1) to obtain the product. A second column, using the same eluents, was required to obtain pure *1,4,8,11,15,18,22,25-octakis(decyl)phthalocyaninato-dihydroxysilicon* (130 mg, 76.7 μmol, 64%) [^{1}H NMR (270 MHz, C_6D_6) δ 7.94 (s, 8H), 4.73 (t, 16H), 2.34 (quintet, 16H), 1.8 (quintet, 16H), 1.2-1.6 (m, 96H), 0.87 (t, 24H), -5.74 (br s, 2H) ppm. λ_{max} ($\varepsilon x10^5$) 703 (2.5) nm in THF. MALDI-MS: isotopic clusters at 1696 [M^+, 30%] and 1679 [M^+-H_2O, 100%]. Found: C, 79.38; H, 10.64; N, 6.33%. $C_{112}H_{178}N_8O_2Si$ requires: C, 79.28; H, 10.57; N, 6.6%].

General procedure for other silicon phthalocyanine derivatives:

To a stirred mixture of metal-free phthalocyanine and tri-n-butylamine in dichloromethane was added trichlorosilane (excess) via a syringe directly into the solution. The resulting mixture was stirred for 16 hours under Ar. The solution was then poured into water (200 ml) with stirring. To the resulting mixture was added triethylamine (60 ml)

slowly. The resulting precipitate was then filtered off and washed with dichloromethane. The organic layer from the filtrate was washed with 20% aqueous HCl (4×100 ml), water (2×100 ml), brine, dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The resulting product was purified by column chromatography.

Preparation of [1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)-phthalocyaninato]dihydroxysilicon (compound number **10**):

The above procedure was followed using 1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine (300 mg, 0.186 mmol), tri-n-butylamine (20 ml), trichlorosilane (2 ml) and dichloromethane (60 ml). The resulting greenish-blue product was purified by column chromatography (silica gel, eluent: petroleum ether /DCM 3:1). The eluent was then changed by increasing the DCM to afford [1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyaninato]-dihydroxysilicon (160 mg, 51%) as a waxy green solid [Found: C, 77.37; H, 9.87; N, 6.43%; $C_{107}H_{160}N_8O_5Si$ requires: C, 77.11; H, 9.68; N, 6.72%. MALDI-MS: isotopic cluster at 1666 (20%, M^+) and 1649 (100%, M-H_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 7.89-7.91 (6H, m), 7.62 (1H, s), 7.44-7.53 (3H, m), 7.01 (1H, dd, J 7.7 and 2.2), 4.57-4.70 (6H, m), 4.45 (8H, m), 4.22 (2H, t, J 7.0), 3.94 (3H, s), 1.99-2.28 (16H, m), 0.95-1.79 (91H, m), 0.69-0.82 (18H, m), 0.58 (3H, t, J 7.3) ppm. λ_{max} (6×10^{-6} M in THF) 719nm ($\varepsilon = 2.16\times10^5$)].

Preparation of [1,4-dibutoxy-2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)-phthalocyaninato]dihydroxysilicon (compound number **13**):

The above procedure was followed using 1,4-dibutoxy-2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine (250 mg, 0.146 mmol), tri-n-butylamine (20 ml), trichlorosilane (1.5 ml) and dichloromethane (60 ml). The resulting greenish-blue product was purified by column chromatography (silica gel, eluent: petroleum ether /DCM 1:1) to afford [1,4-dibutoxy-2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)-phthalocyaninato]dihydroxysilicon (170 mg, 65%) as a waxy greenish blue solid [Found: C, 77.39; H, 9.47; N, 6.08%; $C_{114}H_{166}N_8O_6Si$ requires: C, 77.24; H, 9.44; N, 6.08%. MALDI-MS: isotopic cluster at 1772 (60%, M^+) and 1754 (100%, M-H_2O). ^1H NMR (270 MHz, $CDCl_3$) δ 7.97-8.01 (6H, m), 7.30 (2H, d, J 7.9), 7.16 (2H, m), 7.00 (2H, m), 6.89 (2H, dd, J 8.35 and 2.64), 4.50-4.60 (12H, m), 4.26 (4H, m), 3.77 (6H, s), 2.19-2.24 (12H,

m), 1.83-1.90 (4H, m), 1.25-1.66 (76H, m), 0.82-1.05 (22H, m), 0.64 (6H, t, J 7.3) ppm. λ_{max} (2.22 $\times 10^{-6}$ M in THF) 715nm (ε= 2.93$\times 10^{5}$)].

Preparation of [1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-methoxyphenyl)-22,25-di(decyl)phthalocyaninato]dihydroxysilicon (compound number **22**):

The above procedure was followed using 1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-methoxyphenyl)-22,25-di(decyl)phthalocyanine (150 mg, 0.08 mmol), tri-n-butylamine (20 ml), trichlorosilane (1.5 ml) and dichloromethane (60 ml). The resulting green product was purified by column chromatography (silica gel, eluent: petroleum ether /THF 4:1) to afford [1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-methoxyphenyl)-22,25-di(decyl)phthalocyaninato]-dihydroxysilicon (95 mg, 61%) [MALDI-MS: isotopic cluster at 1924 (15%, M^+) and 1906 (100%, M-H_2O). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.97 (2H, s), 7.21-7.29 (6H, m), 7.16 (4H, m), 6.97-7.04 (8H, m), 6.80-6.86 (6H, m), 4.68 (12H, m), 4.32 (4H, m), 3.74 (18H, brs), 2.16 (4H, m), 0.61-1.76 (76H, m) ppm; λ_{max} (2.07$\times 10^{-6}$ M in THF) 742nm (ε=1.53$\times 10^{5}$)].

Preparation of 1,4-dibutyloxy-2-bromo-8,11,15,18,22,25-hexakis(decyl) phthalocyaninato-dihydroxysilicon (compound number **31**):

The above procedure was followed using metal-free 1,4-dibutyloxy-2-bromo-8,11,15,18,22,25-hexakis(decyl)phthalocyanine (230 mg, 0.15 mmol), tri-n-butylamine (3 ml) and trichlorosilane (1.5 ml) in dry dichloromethane (15 ml). The resulting product was purified by column chromatography on silica (eluent: petroleum ether (bp. 40-60°C)/THF 10:1) to afford *1,4-dibutyloxy-2-bromo-8,11,15,18,22,25-hexakis(decyl) phthalocyaninato-dihydroxysilicon* as a green solid (100 mg, 0.06 mmol, 42%) [^{1}H NMR (300 MHz, C_6D_6) δ 7.94 (m, 6H), 7.75 (s, 1H), 4.92 (m, 4H), 4.71 (m, 8H), 4.5 (t, 2H), 4.27 (t, 2H), 2.35 (m, 12H), 1.2-2.2 (m, 92H), 1.0 (m, 6H), 0.82 (m, 18H), -5.77 (s, 2H) ppm. λ_{max} (εx10^5) 718 (1.55) nm in THF. MALDI-MS: isotopic clusters at 1639 [M^+, 20%] and 1623 [M^+-H_2O, 100%]. Found: C, 73.38; H, 9.48; N, 6.3%. $C_{100}H_{153}N_8O_2BrSi$ requires: C, 73.27; H, 9.41; N, 6.83%].

Preparation of [1,4-bis(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)-phthalocyaninato]dihydroxysilicon (compound number **29**):

The above procedure was followed using 1,4-bis(3-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyanine (0.28 g, 0.178 mmol), tri-n-butylamine (15 ml) and trichlorosilane (1.5 ml). The resulting green product was purified by column chromatography on silica (eluent: petroleum ether/THF 10:1) to afford *[1,4-bis(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(decyl)phthalocyaninato]dihydroxysilicon* (101 mg, 35%) [MALDI-MS: isotopic cluster at 1628 [M^+, 28%] and 1611 [M^+-H_2O, 100%]. λ_{max} ($\varepsilon x10^5$) 711 (1.45) nm in THF. Found: C, 78.76; H, 9.7; N, 5.89%. $C_{106}H_{150}N_8O_4Si$ requires: C, 78.18; H, 9.28; N, 6.88%].

Preparation of [1,4-dibutoxy-2-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)-phthalocyaninato]dihydroxysilicon (compound number **33**):

The above procedure was followed using 1,4-dibutoxy-2-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine (130 mg, 0.1048 mmol), tri-n-butylamine (12 ml) and trichlorosilane (0.5 ml) in dichloromethane (35 ml). The resulting green product was purified by column chromatography (silica gel, eluent: petroleum ether (b.p. 40-60°C)/THF 4:1, then changed to 3:1) to afford *[1,4-dibutoxy-2-(4-pyridyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyaninato]dihydroxysilicon* (50 mg, 36%) [MALDI-MS: isotopic cluster at 1283 (M^+, 25%) and 1300 (M^+-H_2O, 100%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, 2H, J 5.4), 7.94-7.99 (m, 8H), 7.64 (s, 1H), 4.77 (m, 6H), 4.63 (t, 2H, J 7.6), 4.51 (m, 6H), 4.37 (t, 2H, J 7.1), 2.31 (quintet, 2H, J 7.4), 2.18 (m, 12H), 1.85 (m, 2H), 1.62 (m, 12H), 1.17-1.34 (m, 28H), 1.11 (t, 3H, J 7.3), 0.85 (m, 18H), 0.65 (t, 3H, J 7.3) ppm (the OH protons could not be observed). λ_{max} (1.5×10^{-6} M in THF) 720 ($\varepsilon = 1.59 \times 10^5$) nm].

Preparation of [1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)-phthalocyaninato]dihydroxysilicon (compound number **27**):

The above procedure was followed using 4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine (100 mg, 0.787 mmol), tri-n-butylamine (15 ml) and trichlorosilane (0.8 ml) in dichloromethane (50 ml). The resulting greenish-blue product was purified by column chromatography (silica gel, eluent: n-hexane/THF 10:1) to afford *[1,4-dibutoxy-2-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)-phthalocyaninato]dihydroxysilicon* as a waxy green product (50 mg, 48%) [Found: C, 74.80; H, 8.80; N, 7.13%. $C_{83}H_{112}N_8O_5Si$ requires: C, 74.96; H, 8.49; N, 8.43%. MALDI-MS: isotopic cluster at 1329 (M^+, 70%) and 1313 (M^+-H_2O, 100%). ^1H NMR (270 MHz, $CDCl_3$)

δ 7.98 (m, 6H), 7.69 (s, 1H), 7.51-7.59 (m, 3H), 7.09 (dd, 1H, J 7.7 and 2.1), 4.64-4.78 (m, 6H), 4.48-4.57 (m, 8H), 4.29 (t, 2H, J 6.8), 4.01 (s, 3H), 2.09-2.34 (m, 14H), 1.19-1.85 (m, 40H), 1.11 (t, 3H, J 7.3), 0.75-0.98 (m, 18H), 0.65 (t, 3H, J 7.3), -5.37 (br s, 2H) ppm. λ_{max} (3×10^{-6} M in THF) 719 ($\varepsilon = 1.73\times10^{5}$) nm].

Preparation of [1,4-dibutoxy-2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)-phthalocyaninato]dihydroxysilicon (compound number **35**):

The above procedure was followed using 2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)phthalocyanine (150 mg, 0.109 mmol), tri-n-butylamine (20 ml) and trichlorosilane (1 ml) in dichloromethane (60 ml). The resulting greenish-blue product was purified by column chromatography (silica gel, eluent: n-hexane/THF 10:1) to afford *[1,4-dibutoxy-2,3-di-(m-methoxyphenyl)-8,11,15,18,22,25-hexakis(hexyl)-phthalocyaninato]dihydroxysilicon* as a waxy greenish blue product (70 mg, 45%) [Found: C, 75.25; H, 8.42; N, 7.46%. $C_{90}H_{118}N_8O_6Si$ requires: C, 75.27; H, 8.28; N, 7.80%. MALDI-MS: isotopic cluster at 1436 (M^+, 45%) and 1419 (M^+-H_2O, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (m, 6H), 7.18-7.22 (m, 2H), 7.07 (m, 2H), 6.91 (m, 2H), 6.78 (dd, 2H, J 8.4 and 2.2), 4.41-4.50 (m, 12H), 4.18 (m, 4H), 3.68 (s, 6H), 2.09-2.14 (m, 12H), 1.77 (m, 4H), 1.18-1.60 (m, 36H), 0.75-0.95 (m, 22H), 0.55 (t, 6H, J 7.3), -5.3 (br s, 2H) ppm. λ_{max} (2.8×10^{-6} M in THF) 715 ($\varepsilon = 2.11\times10^{5}$) nm].

Preparation of [1,4,8,11-tetrabutoxy-2,3,9,10-tetra-(m-methoxyphenyl)-15,18,22,25-tetrakis-hexyl)phthalocyaninato]dihydroxysilicon (compound number **36**):

The above procedure was followed using 1,4,8,11-tetrabutoxy-2,3,9,10-tetra-(m-methoxyphenyl)-15,18,22,25-tetrakis(hexyl)phthalocyanine (90 mg, 0.0575 mmol), tri-n-butylamine (15 ml) and trichlorosilane (0.8 ml) in dichloromethane (50 ml). The resulting greenish-blue product was purified by column chromatography (silica gel, eluent: n-hexane/ THF 9:1) to afford *[1,4,8,11-tetrabutoxy-2,3,9,10-tetra-(m-methoxyphenyl)-15,18,22,25-tetrakis(hexyl)phthalocyaninato]dihydroxysilicon* (40 mg, 43%) [Found: C, 73.37; H, 7.45; N, 6.54%. $C_{100}H_{122}N_8O_{10}Si$ requires: C, 73.95; H, 7.57; N, 6.90%. MALDI-MS: isotopic cluster at 1624 (M^+, 22%) and 1607 (M^+-H_2O, 100%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.99 (m, 4H), 6.98-7.23 (m, 12H), 6.84 (m, 4H), 4.77 (m, 8H), 4.51 (t, 4H, J 6.8), 4.27 (m, 4H), 3.75 (s, 6H), 3.74 (s, 6H), 2.06-2.24 (m, 8H), 1.85 (m, 4H), 0.85-1.72 (m, 48H), 0.76 (t, 6H,

J 7.3), 0.66 (t, 6H, J 7.3) ppm (the OH protons could not be observed). λ_{max} (2.4 $\times 10^{-6}$ M in THF) 723 ($\varepsilon = 1.95 \times 10^5$) nm].

Preparation of [1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-methoxyphenyl)-22,25-di(hexyl)phthalocyaninato]dihydroxysilicon (compound number **37**):

The above procedure was followed using 1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-methoxyphenyl)-22,25-di(hexyl)phthalocyanine (60 mg, 0.0342 mmol), tri-n-butylamine (12 ml) and trichlorosilane (0.5 ml) in dichloromethane (50 ml). The resulting green product was purified by column chromatography (silica gel, eluent: n-hexane/THF 4:1) to afford *[1,4,8,11,15,18-hexabutoxy-2,3,9,10,16,17-hexa-(m-methoxyphenyl)-22,25-di(hexyl)phthalocyaninato]dihydroxysilicon* (30 mg, 46%) [MALDI-MS: isotopic cluster at 1812 (M^+, 42%) and 1795 (M^+-H_2O, 100%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.99 (s, 2H), 6.98-7.22 (m, 18H), 6.81-6.87 (m, 6H), 4.73 (m, 12H), 4.30 (m, 4H), 3.74 (s, 6H), 3.75 (s, 12H), 2.17 (m, 4H), 0.78-1.76 (m, 42H), 0.75 (t, 12H, J 7.3), 0.67 (t, 6H, J 7.3) ppm (the OH protons could not be observed). λ_{max} (2.07$\times 10^{-6}$ M in THF) 742 ($\varepsilon = 1.53 \times 10^5$) nm].

The following dihydroxysilicon compounds were prepared similarly:
[1,4,8,11-tetrabutoxy-2,3,9,10-tetra-(m-methoxyphenyl)-15,18,22,25-tetrakis(decyl)-phthalocyaninato]dihydroxysilicon (compound number **16**) [MALDI-MS: isotopic cluster at 1831 (100%, M-H_2O)], [1,4,15,18-tetrabutoxy-2,3,16,17-tetra-(m-methoxyphenyl)-8,11,22,25-tetrakis(decyl)phthalocyaninato]dihydroxysilicon and [1,4,8,11,15,18,22,25-octabutoxy-2,3,9,10,16,17,23,24-octa-(m-methoxyphenyl)phthalocyaninato]dihydroxy silicon.

B. Biological Experimental Details

Use of cell inactivation studies

In order to demonstrate that the compounds being studied also possess the ability to act as efficient photosensitizer of biological systems, cells were incubated with the compound of interest, formulated in a liposome suspension, and then exposed to light of a suitable wavelength and energy. The number of viable cells surviving this treatment was registered.

The cell line chosen is the HT 1080 fibrosarcoma cell line [ATCC number: CCL-1212. (Reference: S. Rasheed, W.A. Nelson-Rees, E.M. Toth, P. Arnstein, M.B. Gardner, "Characterisation of a newly derived human sarcoma cell line (HT-1080)", *Cancer*, vol. 33, pages 1027-1033, 1974)]. This cell line represents hyperproliferating cells and is thus a useful model for the rapid cell cycle occurring in psoriasis.

Preparation of liposomes

Reference: G. Valduga, G. Bianco, G. Csik, E. Reddi, L. Masiero, S. Garbisa, G. Jori "Interaction of hydro- or lipophilic phthalocyanines with cells of different metastatic potential" *Biochem. Pharmacol.*, vol. 51, pages 585-590, 1996.

Formulation of compounds in unilamellar liposomes of L-α-dioleoyl-phosphatidylcholine (DOPC). The procedure developed can be schematised as follows:

1. A stock solution of DOPC in chloroform is prepared at a concentration of 20 mg/ml.
2. 4ml from such solution are introduced into a 250ml glass flask connected to a Rotavapor, and mixed with a suitable volume of the compound in solution in tetrahydrofuran (THF) to reach a final molar ratio 1:200 between the phthalocyanine and the phospholipid. The flask is wrapped with aluminium foil.
3. The flask is saturated with nitrogen and kept at room temperature for 5 minutes.
4. The Rotavapor is then connected to a water pump in order to generate reduced pressure and the solvent is evaporated at room temperature.
5. The flask is saturated with nitrogen and 4ml of nitrogen-saturated phosphate buffered saline (PBS) are added. The lipid film containing the phthalocyanine is resuspended by gently shaking in the presence of glass beads.
6. The aqueous suspension is sonicated (10 Hz) for about 30 minutes. The vial is saturated with nitrogen and kept in an ice bath. At the end the liposomes are kept at room temperature overnight.

The liposomes have a shelf-life at 4°C of at least three months. Before use, they are filtered through a 0.2 μm filter and the phthalocyanine concentration is measured by

diluting a small aliquot of the suspension into a known excess of THF and determining the absorbance of such solution.

Cell studies

The cells were routinely cultured with DMEM (Eagle's modified Dulbecco medium added with 100 units/ml penicillin, 100 μg/ml streptomicin, 0.25 μm/ml anfotericin, 2mM glutamine) containing 10% FCS (foetal calf serum) and maintained in a humid atmosphere containing 5% CO_2 at a temperature of 37°C. Normally, the cells were detached by using a solution of 0.05% trypsin - 0.02% EDTA in phosphate-buffered saline. The action of trypsin was blocked by addition of FCS. The cell pellet, obtained by centrifugation at 1,000 rpm for 8 minutes was resuspended with DMEM and 10% FCS and then seeded in 75 cm^2 tissue cultured flasks.

Cell uptake of phthalocyanine

In a typical experiment, $6x10^5$ cells were suspended in DMEM (Eagle's modified Dulbecco medium) containing 10% FCS (foetal calf serum) and incubated in 25 cm^2 tissue culture flasks. After 24 hours the culture medium was removed and replaced by 5ml DMEM (enriched with 3% FCS) containing either 5 μM or 10 μMof the phthalocyanine. The phthalocyanine was added in an aqueous suspension of DOPC liposomes. After 1 hour incubation, the medium was removed, the cells were washed twice with 4ml of PBS devoid of Ca^{2+} and Mg^{2+} ions.

The cell pellet was homogenised with 2% aqueous sodium dodecylsulphate (SDS) (2ml). The suspension thus obtained was divided into two portions:

a) 1ml was diluted with a known volume of THF for the determination of the phthalocyanine concentration by spectrophotofluorimetric analysis (excitation at 650 nm, emission collected in the 660-780 nm interval)using a Perkin-Elmer LS50B spectrophotofluorimeter.

b) 0.5ml was used for the determination of the protein content by the standard assay with bicinchoninic acid.

Reference: P.K. Smith, "Measurement of protein using bicinchoninic acid", *Anal. Biochem.*, vol. 150, pages 76-85, 1985.

The amount of phthalocyanine recovered was calculated by interpolation with a calibration plot and the uptake was expressed as nmoles of phthalocyanine/mg of cell protein.

Cell irradiation studies

For irradiation studies, $1.8x10^5$ cells were seeded in Petri dishes of 7cm diameter, incubated for 24 hours in DMEM containing 10% FCS in a humid atmosphere containing 5% CO_2 and at a temperature of 37°C. The medium was removed and replaced by 1ml DMEM containing 2.5 μM to 10 μM phthalocyanine which was added in DOPC liposomes. After 1 hour incubation, the cells were washed twice with PBS containing Ca^{2+} (0.9 mM $CaCl_2 \cdot 2\ H_2O$) ions and Mg^{2+} (0.5 mM $MgCl_2 \cdot 2\ H_2O$) ions.

Light source

The light source – Waldmann PDT 1200 (Waldmann Medical Division, Villingen-Schwenningen, Germany) – is a non-coherent light source with a filter allowing light between 600 and 730 nm to pass. A built-in output meter is used to monitor the doses given. The lamp was operated at a fluence rate of 100 mW/cm^2.

The cells in the Petri dish were irradiated (100 mW/cm^2) for 1, 5, 10, 15 minutes (6 up to 90 J/cm^2) with 1ml PBS containing Ca^{2+} and Mg^{2+} ions.

The irradiated cells were mixed with 2ml DMEM containing 10% FCS and incubated overnight. The photosensitised cells were assayed by the trypan blue test (Reference: C. Milanesi, F. Sorgato, G. Jori, "Photokinetic and ultrastructural studies on porphyrin photosensitization of HeLa cells", *Int. J. Radiat. Biol.*, vol. 55, pages 59-69, 1989) and the survival was expressed as the percentage of the survival typical of cells which had been treated by an identical procedure but were not exposed to light. Preliminary studies showed that irradiation of the cells in the absence of the

photosensitizer and dark incubation of the cells with phthalocyanines has no effect on cell survival.

Photosensitised inactivation of human fibroblasts by phthalocyanines

Table 2 below summarises the in vitro cell survival data obtained in the above described experiments. Substituents R1 to R9 are defined as shown in formula (VIII) below.

C. Photophysical Experimental Details

UV-Vis Spectral Measurement

UV-Vis spectra were recorded using a Hitachi U-3000 Spectrophotometer. The phthalocyanines samples were dissolved in THF, unless otherwise stated, and held in a 1cm x 1cm quartz cuvette. The data were recorded at ambient temperature, 20-23°C.

Fluorescence Spectral Measurements

Fluorescence spectra were recorded using a Hitachi U-4500 Fluorescence Spectrophotometer. The phthalocyanines samples were dissolved in THF and held in a 1cm x 1cm quartz cuvette. The data were recorded at ambient temperature, 20-23°C.

Singlet Oxygen Quantum Yields, Φ_Δ

The singlet oxygen quantum yields were determined by the direct measurement of singlet oxygen phosphorescence at 1270nm using the method described by Nonell (S. Nonell and S. Braslavzky, "Time Resolved Singlet Oxygen Detection", in *Singlet Oxygen, UV-A and Ozone, Methods in Enzymology*, vol. 319, Academic Press, 2000). Samples were excited using the third harmonic of a Q-switched Nd:YAG laser, λ_{ex} = 355nm, (Spectra Physics GCR-150-10). A small fraction of the laser output was passed through a solution state filter containing aqueous $CoSO_4$ to remove residual 532 and 1064nm radiation and then into the sample holder. The samples were held in a 1cm x 1cm fluorescence cuvette (Hellma). During the course of the experiments the incident laser

energy for each measurement was determined using a pyroelectric detector held behind the sample. The laser energy was adjusted by placing cells containing aqueous sodium nitrite between the $CoSO_4$ filter and the light guide. Typical pulse energies used here were in the range 25-500μJ per pulse, as measured using a second, calibrated pyroelectric detector, (Gentec ED-100). Shot to shot noise was estimated to be <10% and sets of 20 shots gave an average value within <3%.

Phosphorescence from the sample was collected and passed through an interference filter centred at 1270nm (Infra Red Engineering Ltd) and then focussed onto the active area of a liquid nitrogen cooled germanium photodiode (North Coast EO-817P). The signal form the detector was AC coupled to a digital oscilloscope (Tektronix TDS-320) which digitised and averaged the transients. Typically 32 laser shots were used for each sample. The averaged data was transferred to a PC where it was stored and analysed.

Stock solutions of the materials were prepared by taking a small sample of the materials supplied and dissolving them in toluene (Fischer Scientific, Analytical grade) containing 1%(v/v) pyridine. The pyridine was added to ensure that the samples did not aggregate. Exact concentrations of these solutions were not determined. Working solutions were prepared by dilution of the stock with toluene to give absorbances of 0.01-0.100 at 355nm when placed in a UV-Vis spectrometer (ATI-Unicam UV-2) compared to a reference cell containing the pure solvent. UV-Vis spectra were recorded in long pathlength cells (2cm) to ensure a more accurate measure of absorbance. Care was taken to avoid high absorbances in the region of the Q-bands (600-750nm) where re-absorption of the fluorescence from the sample can lead to error.

The data were recorded at ambient temperature, 20-23°C, and the solutions were aerated. The singlet oxygen emission decay was recorded for each sample using 5 laser energies and the data for each measurement were fitted to an exponential decay of the form $I(t) = A.\exp(-t/\tau)$ using a fitting function which optimised both A and τ. A typical decay is shown below. A plot of A v's incident laser energy was drawn for each solution and the slope determined. The slope is proportional to the singlet oxygen quantum yield and the amount of light absorbed by the sample. The slope of the graph for each sample was taken and plotted against $(1-10^{-A})$, where A is the absorbance of the samples at the excitation

wavelength. The slope of this graph is then proportional to the singlet oxygen quantum yield.

Experimental errors

The dominant sources of error in the experiment include the shot-to-shot fluctuations in the laser and errors in the measured sample absorbances. For these reasons we are reporting values to have an error of ± 10%.

Standards/ Reference Materials

The values reported here (see Figures 1 to 3) have been recorded relative to perinaphthenone, which has been reported to have a quantum yield of 0.97 (S. Nonell and S. Braslavzky, "Time Resolved Singlet Oxygen Detection", in *Singlet Oxygen, UV-A and Ozone, Methods in Enzymology*, vol. 319, Academic Press, 2000; F. Wilkinson, W.P. Helman and A.B. Ross, "Quantum yields for the photosensitised production of the lowest excited singlet state of molecular oxygen in solution", *J. Phys. Chem. Ref Data.*, vol. 22, pages 113-262, 1993). Wilkinson et al.'s review of singlet oxygen quantum yields contains a number of values for this material, ranging from 0.95-0.97. For this reason there may be a small error in the absolute value, but the trends in the reported yields are significant.

Singlet Oxygen Quantum Yields: Results

Values are reported relative to the standard perinaphthenone, $\Phi_\Delta = 0.97$ (S. Nonell and S. Braslavzky, "Time Resolved Singlet Oxygen Detection", in *Singlet Oxygen, UV-A and Ozone, Methods in Enzymology*, vol. 319, Academic Press, 2000). As discussed above the recorded values have an error of ± 10%.

Fluorescence Lifetimes

Fluorescence lifetimes were determined using the method of time-correlated single photon counting (*Principles of Fluorescence Spectroscopy 2nd Ed*, J. Lakowicz, Kluwer Academic/ Plenum Press). Samples were excited using the output from a 635nm pulsed

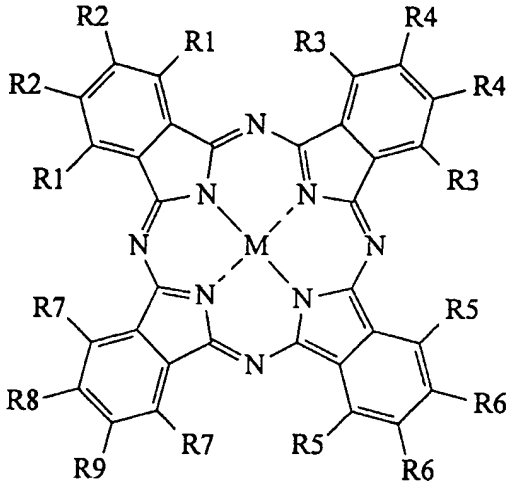
diode laser (IBH NanoLed). This produced a 1MHz train of pulses with a FWHM of 200ps. Fluorescence was collected at 90° to the excitation source and the emission wavelength selected by a monochromator (Jobin-Yvon Triax 190) and detected using a cooled red-sensitive photomultiplier/discriminator (IBH TXB-04). The output from the detector was used as the start signal for a time to amplitude converter (Ortec 567) and the stop signal was derived from the laser power supply/driver. The TAC output was processed by a pulse height analyser (Ortec Trump 8K). Typically decays were obtained using a record length of 1024 channels with a time-window of 55ps/channel. Instrument response functions were obtained using a scattering suspension and were typically 450ps FWHM. Decays were analysed by the method of iterative reconvolution of the response function with a sum-of-exponentials and the fit optimised by the method of non-linear least-squares analysis. The quality of fit was judged by the reduced chi-squared, randomness of residuals and auto-correlation function (*Principles of Fluorescence Spectroscopy 2nd Ed*, J. Lakowicz, Kluwer Academic/ Plenum Press).

Fluorescence Quantum Yields

Florescence quantum yields were determined using the relative method. Spectra were recorded using a Jobin-Yvon Fluoromax-2 spectrofluorimeter and were corrected for background and the spectral response of the instrument. Samples were compared to the following standard materials: quinine sulfate in 1M sulfuric acid, Φ_f = 0.55 and Rhodamine 101 in acidified ethanol Φ_f = 1.00.

Photophysical data for examples of silicon, zinc and metal-free substituted phthalocyanines

Table 2 below summarises the results obtained in the above described photophysical experiments. Substituents R1 to R9 are defined as shown in formula (VIII) below.



(VIII)

Compound Number	R1	R2	R3	R4	R5	R6	R7	R8	R9	M	λ_{max} abs nm (THF)	λ_{max} em nm (THF)	Φ_Δ ±10%	Φ_f ±10%	τ_f ±5%	In vitro Cell Survival as % after Continuous Irradiation for		
																5 min	10 min	15 min
1	C_5H_{11}	H	C_5H_{11}	H	C_5H_{11}	H	C_5H_{11}	H	H	$Si(OH)_2$	703	721.4 792.6(s)	0.51	*a*	3.7	2.2±1.4	1.3±0.6	0.9±0.1
2	C_5H_{11}	H	C_5H_{11}	H	C_5H_{11}	H	C_5H_{11}	H	H	Zn	700	709.2	0.69	*a*	2.0	84.4±3.8	48.5±15.9	28.0±13.4
3	C_6H_{13}	H	C_6H_{13}	H	C_6H_{13}	H	C_6H_{13}	H	H	$Si(OH)_2$	704	709.8	0.50	*a*	3.71	0.5±0.2	<0.1	<0.1
4	C_6H_{13}	H	C_6H_{13}	H	C_6H_{13}	H	C_6H_{13}	H	H	Zn	700.5	*a*	0.60	*a*	1.9	3.7±1.2	0.5±0.1	0.1±0.1
5	C_8H_{17}	H	C_8H_{17}	H	C_8H_{17}	H	C_8H_{17}	H	H	$Si(OH)_2$	703.5	722.6 794.2(s)	0.33	*a*	*a*	49.8±0.7	2.0±1.9	0.3±0.1
6	C_8H_{17}	H	C_8H_{17}	H	C_8H_{17}	H	C_8H_{17}	H	H	Zn	700.5	708.8	0.57	*a*	*a*	80.1±4.3	57.9±17.7	41.9±2.0
7	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	H	$Si(OH)_2$	703	722.2 798.0(s)	0.37	*a*	*a*	45.4±3.1	3.2±1.0	0.5±0.2
8	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	H	Zn	700	710	0.66	0.26	1.67	31.1±2.2	0.4±0.3	<0.1
10	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	OC_4H_9	m-MeO-C_6H_4	H	$Si(OH)_2$	719	709.8(s) 738.0 810(s)	0.42	*a*	*a*	0.5±0.3	<0.1	<0.1
11	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	OC_4H_9	m-MeO-C_6H_4	H	Zn	715	709.2 729.2(s)	0.55	*a*	*a*	75.0±5.7	62.0	13.3±0.8
13	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	$Si(OH)_2$	715	735.6 808.8(s)	0.47	*a*	*a*	3.8±0.8	0.9±0.2	<0.1
14	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	Zn	712	709.8(s) 728.6 789.0(s)	0.59	*a*	*a*	81.3±10.5	38.4±8.7	17.5±6.8

Compound Number	R1	R2	R3	R4	R5	R6	R7	R8	R9	M	λ_{max} abs nm (THF)	λ_{max} em nm (THF)	Φ_Δ ±10%	Φ_f ±10%	τ_f ±5%	In vitro Cell Survival as % after Continuous Irradiation for		
																5 min	10 min	15 min
16	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	$Si(OH)_2$	*a*	*a*	0.37	*a*	*a*	*a*	*a*	*a*
17	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	Zn	719	709.4(s) 741.0 804.2(s)	0.38	*a*	*a*	87.0±12.3	82.0±20.4	72.5±13.4
22	$C_{10}H_{21}$	H	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	$Si(OH)_2$	742	*a*	*a*	*a*	*a*	*a*	*a*	*a*
23	$C_{10}H_{21}$	H	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	Zn	732	*a*	*a*	*a*	*a*	98.7±0.8	87.9±14.2	54.9±12.2
27	C_6H_{13}	H	C_6H_{13}	H	C_6H_{13}	H	OC_4H_9	m-MeO-C_6H_4	H	$Si(OH)_2$	719	*a*	0.35	*a*	*a*	76.9±14.8	59.0±9.3	51.1±18.8
28	C_6H_{13}	H	C_6H_{13}	H	C_6H_{13}	H	OC_4H_9	m-MeO-C_6H_4	H	Zn	714	*a*	0.45	*a*	*a*	0.2±0.1	<0.1	<0.1
29*	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	m-MeO-C_6H_4	H	H	$Si(OH)_2$	711	*a*	*a*	*a*	*a*	2.11±0.9	<0.1	<0.1
30	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	m-MeO-C_6H_4	H	H	Zn	710	722.4	*a*	*a*	*a*	80.8±1.7	3.9±0.8	<0.1
31	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	OC_4H_9	Br	H	$Si(OH)_2$	718	709.8(s) 736.2 809.2(s)	0.46	*a*	*a*	9.0±0.7	0.5±0.2	<0.1
32	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	$C_{10}H_{21}$	H	OC_4H_9	Br	H	Zn	716.5	*a*	*a*	*a*	*a*	75.2±1.3	12.5±5.2	0.3±0.1

Compound Number	R1	R2	R3	R4	R5	R6	R7	R8	R9	M	λ_{max} abs nm (THF)	λ_{max} em nm (THF)	Φ_Δ ±10%	Φ_f ±10%	τ_f ±5%	In vitro Cell Survival as % after Continuous Irradiation for		
																5 min	10 min	15 min
33	C_6H_{13}	H	C_6H_{13}	H	C_6H_{13}	H	OC_4H_9	4-pyridyl	H	$Si(OH)_2$	720	709.2(s) 738.8 813.8(s)	0.29	*a*	*a*	4.5±1.2	0.2±0.1	<0.1
34	C_6H_{13}	H	C_6H_{13}	H	C_6H_{13}	H	OC_4H_9	4-pyridyl	H	Zn	718	709.4(s) 735.0	0.64	*a*	*a*	45.0±8.0	0.5±0.2	<0.1
35	C_6H_{13}	H	C_6H_{13}	H	C_6H_{13}	H	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	$Si(OH)_2$	715	710(s) 734.8 810.8(s)	0.49	*a*	*a*	16.4±3.3	0.2±0.1	<0.1
36	C_6H_{13}	H	C_6H_{13}	H	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	$Si(OH)_2$	723	708.6(s) 744.8 809.2	*a*	*a*	*a*	12.6±7.0	0.4±0.3	<0.1
37	C_6H_{13}	H	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	$Si(OH)_2$	742	*a*	*a*	*a*	*a*	*a*	*a*	*a*
38	C_6H_{13}	H	C_6H_{13}	H	C_6H_{13}	H	OC_4H_9	4-pyridyl	4-pyridyl	Zn	719	*a*	*a*	*a*	*a*	83.3±7.9	25.0±2.9	1.2±0.6
20	$C_{10}H_{21}$	H	OC_4H_9	m-MeO-C_6H_4	$C_{10}H_{21}$	H	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	Zn	732 703	*a*	*a*	*a*	*a*	96.4±5.2	84.6±6.2	78.2±0.6
26	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	OC_4H_9	m-MeO-C_6H_4	m-MeO-C_6H_4	Zn	742	*a*	*a*	*a*	*a*	94.5±5.1	70.1±9.1	47.8±23.6

Table 2. – Comparison of silicon- and zinc-containing phthalocyanines.

a = value not measured

* irradiation at 711 nm by a Ti:sapphire laser for measurement of cell survival

D. Biological Activity of silicon(dihydroxy) phthalocyanines

Effects in animal models of restenosis

Restenosis is the formation of a new blockage in arteries following treatment using balloon angioplasty to open up partially blocked arteries. This formation of a second blockage occurs in less than 6 months in up to 50% of patients treated with balloon angioplasty and represents a major clinical problem.

Animal models of restenosis have been developed using rats, rabbits, dogs, pigs etc. The animal models are performed by introducing a balloon catheter into an artery of the animal and producing a lesion in the artery wall, which is very similar to the clinical procedure. The substance of interest is introduced in the region of the lesion, a light guide (catheter coupled to a light source) is introduced and the photosensitiser is activated. Then the degree of new cellular growth into the blood vessel is measured at intervals of days or weeks.

The model used for the purposes of the present invention is described in an article entitled "Local photodynamic therapy with Zn(II)-phthalocyanine in an experimental model of intimal hyperplasia" by A. Visona, A. Angelini, S. Gobbo, A. Bonanome, G. Thiene, A. Pagnan, D. Tonello, E. Bonadini, G. Jori, published in Journal of Photochemistry and Photobiology, B: Biology, vol. 57, 2000, pages 94-101.

The compounds tested were (a) zinc(II) phthalocyanine, formulated in liposomes as described by the authors of "Local photodynamic therapy with Zn(II)-phthalocyanine in an experimental model of intimal hyperplasia", and (b) silicon(dihydroxy) octahexyl phthalocyanine (compound **3** as defined in Table 2), formulated as described in the section entitled "Preparation of liposomes" above. The iliac arteries of groups of 3 rabbits were lesioned as described in "Local photodynamic therapy with Zn(II)-phthalocyanine in an experimental model of intimal hyperplasia" and the animals treated with the compounds, followed by illumination.

The degree of intimal hyperplasia (IH) was evaluated at weekly intervals up to 1 month after PDT treatment (3 rabbits at each time point). Table 3 summarises the results obtained in the above described experiments.

Time	IH %		
	Control	Compound 3	ZnPc*
1 week	17.05 ± 2.16	0.00 ± 0.00	0.00 ± 0.00
2 weeks	30.75 ± 6.78	12.93 ± 4.07	16.89 ± 3.43
3 weeks	59.10 ± 3.40	35.03 ± 4.18	33.28 ± 12.29
4 weeks	68.33 ± 1.16**	43.85 ± 11.00	40.35 ± 7.80

Table 3.
* Data from Visona et al. (2000), 34 rabbits overall
** One rabbit died at 25 days

The doses of the compounds used for treatment were identical and the results obtained indicate that both silicon- and zinc-containing phthalocyanines impede and delay the development of restenosis in the model to a similar degree under the conditions chosen.

Mechanisms of action as measured by Caspase-3 activity in HT 1080 human transformed fibroblasts

The term apoptosis is applied to a group of characteristic structural and molecular events that separate this type of cell deletion from necrosis. In contrast to necrosis which involves a group of cells simultaneously, apoptosis may occur in a single cell surrounded by a group of viable cells. There is a distinct and precisely localised control over the fate of specific cells in a mixed cell population that undergoes apoptosis. Apoptosis is a selective process for deletion of cells in various biological systems. Similar to proliferation, apoptosis is tightly regulated with both processes playing essential roles in the homeostasis of renewable tissues.

Diverse groups of molecules are involved in the apoptosis pathway. One set of mediators implicated in apoptosis belong to the aspartate-specific cysteinyl proteases or caspases. A member of this family, caspase-3 (CPP32, apopain, YAMA) has been identified as being a key mediator of apoptosis of mammalian cells.

In order to investigate the mechanism of action of the silicon- and zinc-containing phthalocyanines, selected phthalocyanines were formulated as described in the section entitled "Preparation of liposomes" above. HT 1080 fibrosarcoma cells were treated with the compounds and exposed to light as described in the sections entitled "Cell irradiation studies" and "Light source" above. The activity of caspase-3 was measured in the PDT-treated cells at various post-treatment times, for which an ApoAlert CPP32 kit (Clontech Palo Alto, CA) was used. According to the manufacturer recommended procedure, 10^6 cells were collected by centrifugation, resuspended in 50 µl of lysis buffer and held on ice for 10 minutes. Then 50 µl of reaction buffer containing DTT and 5 µl of DEVD-AFC were added to the cell lysate and after 1 hour of incubation at 37°C, the fluorescence emitted at 505 nm (λ_{ex} = 400 nm) was measured with a Perkin-Elmer LS50 spectrofluorimeter. The caspase-3 activity in the treated cells was expressed as a percentage of the fluorescence from untreated cells used as reference.

Table 4 shows caspase-3 activity in HT 1080 fibrosarcoma cells irradiated for selected lengths of time in the presence of selected phthalocyanines at a 10 µM concentration. All measurements were performed at 3 hours after irradiation. Compound numbers are as defined in Table 2. Compounds **3** and **29** are $Si(OH)_2$ derivatives, compound **8** is a zinc derivative.

Sample	Irradiation Time	% Fluorescence (Caspase-Activity)
control	-	100 ± 0
compound **8**	15 minutes	870 ± 21
compound **29**	3 minutes	105 ± 20
compound **29**	15 minutes	130 ± 17
compound **3**	3 minutes	180 ± 16
compound **3**	5 minutes	210 ± 43

Table 4.

The results obtained indicate that zinc-containing compound **8** induces a substantially larger expression of caspase-3 and is thus likely to promote a larger degree of

apoptosis, whereas the silicon-containing compounds **3** and **29** appeared to act by a necrosis mechanism.

Uptake of the phthalocyanines into mouse skin and the effects of illumination

In order to evaluate the potential of the silicon-containing phthalocyanines for use in the treatment of skin disorders, a mouse model was used in which the compounds were applied onto the dorsal skin of mice. The amount of phthalocyanine taken up by the skin was determined by extracting the skin sample after euthanising the animal. Defined doses of phthalocyanines were applied onto the skin of mice and irradiated with light of defined properties. The biological effects were then observed for a period of up to 10 days.

The phthalocyanines tested for skin uptake were zinc(II) octahexyl phthalocyanine (compound **4** as defined in Table 2) and silicon(dihydroxy) octahexyl phthalocyanine (compound **3** as defined in Table 2).

Balb/c mice (body weight 19-21 g) were depilated on the dorsal skin by application of a cream. At 24 hours after depilation, 20 μg phthalocyanine in a formulation consisting of:

a) tea tree oil (10 ml)
b) transcutol (45 ml)
c) tetrahydrofuran containing the phthalocyanine (45 ml)
d) densifying factor (Klugel) (10 ml)

(total volume 20 μl) were dropwise deposited on a predetermined 1 cm^2 skin area, while the mice were kept under light anesthesia (intraperitoneal injection of ketalar). After 5 hours, the area where the phthalocyanine had been deposited was washed with a cotton swab, which was wet with physiological solution (PBS), until no further dyeing of the cotton was noticed. Then the mice were sacrificed by prolonged exposure to ether vapours, the deposition skin area was quickly removed and the phthalocyanine content was quantitatively determined by a spectrophotofluorimetric analytical procedure.

The skin (1 cm^2 which was weighed to identify the total mass) was homogenized in a Potter vessel with 2% aqueous SDS (2 ml). The homogenate was magnetically stirred for

1 hour at room temperature. Then 300 µl of the suspension were 10-fold diluted with THF, centrifuged at 3,000 rpm for 10 minutes, the supernatant was collected and the characteristic phthalocyanine fluorescence emission was measured.

The amounts of compounds **3** and **4** recovered from the skin at 5 hours after the end of the topical deposition of the phthalocyanines (20 µg/cm^2) on depilated mouse dorsal skin are reported in Table 5. The average value is 5.8% of the total deposited phthalocyanine for both compounds.

Mouse Number	% Recovery of	
	Compound 3	Compound 4
1	4.0	6.5
2	4.7	5.2
3	8.6	5.8
Average	5.8 ± 2.5	5.8 ± 0.7

Table 5.

The photosensitising activities of compound **3** (as defined in Table 2) and of compound **8** (as defined in Table 2) were tested in mice using the following protocol:

a) phthalocyanine dose: 20 µg/cm^2 of skin area
b) time interval between deposition and irradiation: 5 hours
c) fluence-rate: 400 mW/cm^2
d) total light dose: 300 J/cm^2 (14 minutes, 17 seconds irradiation)
e) light source: diode laser with emission tuned at 670 nm
f) number of mice (Balb/c, female, body weight: 20-22 g) per irradiation session: at least 3

The results of several phototherapeutic experiments carried out are summarised in Table 6.

Compound	Phthalocyanine Dose	Skin Response
compound **8**	20 $\mu g/cm^2$	none to slight
compound **3**	20 $\mu g/cm^2$	oedema, rapidly disappearing within 48 hours
compound **3**	20 $\mu g/cm^2$, topically applied from a stock solution containing 0.5 $\mu g/ml$ of phthalocyanine (total applied volume: 40 μl)	extensive oedema which evolves into a superficial eschar within about 72 hours and gradually heals within one week

Table 6.

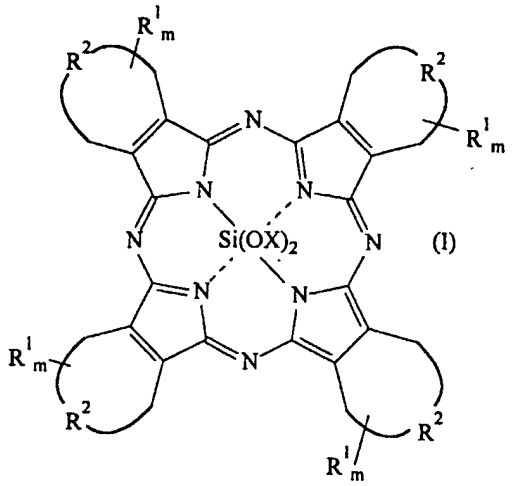
This protocol of steps a) to f) outlined above was selected, because it had given the best skin response to phthalocyanine photosensitization with appearance of extensive oedema in the phthalocyanine-loaded and irradiated skin area, which evolved into a superficial eschar within about 72 hours.

In a second experiment, the total irradiation time was prolonged to 20 minutes (namely 480 J/cm^2) in order to maximise the previously obtained effects. All the four mice in the group sensitised with compound **3** and irradiated, developed an evidently deep eschar within 48 hours after the end of irradiation; no complete healing of the photoinduced lesion was observed at 10 days after PDT. However, further irradiation studies using compound **4** as a skin-photosensitizing agent instead of compound **3** gave no appreciable skin photoresponse.

Thus the results presented in Table 2 (cell survival), Table 4 (caspase-3 activity) and Table 6 (effects on mouse skin), together with the effects on the dorsal skin of mice, indicate that the presence of the silicon ion enhances the photosensitizing activity of the phthalocyanines against both cells and tissues.

Claims:

1. A substituted di(hydroxy/alkoxy)silicon phthalocyanine of formula (I)

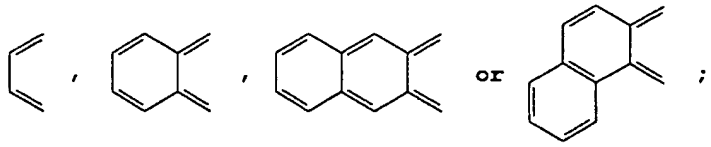


wherein m are the same or different and each m is 0, 1, 2, 3 or 4, provided that not all four m are simultaneously 0;

R^1 are the same or different and each R^1 is C_1-C_{20} alkyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$ and/or $-R^4-N-(R^5)_2$; C_2-C_{20} alkenyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$ and/or $-R^4-N-(R^5)_2$; C_2-C_{20} alkynyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-R^4-N-(R^5)_2$, $-Si(R^5)_3$, $-C_5H_4N$, $-C_4H_3S$ and/or $-C_6H_5$; $-R^4-O-R^5$; $-R^4-S-R^5$; $-R^4-SO_3H$; $-R^4-SO_2R^5$; $-R^4-SO_2N(R^5)_2$; $-R^4-N-(R^5)_2$; $-R^4-P-(R^5)_2$; $-R^4-P(O)(OR^5)_2$; $-R^4$–aryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-OR^5$, $-SO_3H$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$; $-R^4$–heteroaryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$; $-R^4-COR^5$; $-R^4-COOR^5$; $-R^4-CON(R^5)_2$; –F; –Cl; –Br; –I or $-B(OH)_2$; where

$-R^4-$ are the same or different and each $-R^4-$ is a chemical bond, $-(CH_2)_q-$ with q being an integer from 1 to 20, or $-(CH_2)_aCH=CH(CH_2)_b-$ with a and b being integers from 0 to 20 and the sum of a and b being from 0 to 20; and $-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl optionally substituted, hetereoaryl optionally substituted or H, or two $-R^5$ together form a saturated or unsaturated ring;

R^2 are the same or different and each R^2 is



X are the same or different and each X is –H, $-CH_3$ or $-CH_2CH_3$,

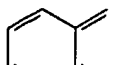
provided that not on all four substituent-units simultaneously have

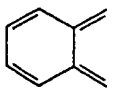
R^2 =  , one non-peripheral $R^1 = -(SCH_2CH_2)_3-N(CH_2CH_3)_2$, one non-peripheral R^1 = –Cl, and both peripheral $R^1 = -O\text{-}C_6H_4\text{-}p\text{-}Cl$, or

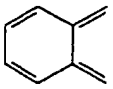
R^2 =  , one non-peripheral $R^1 = -O^iC_5H_{11}$, one non-peripheral $R^1 = -O^iC_4H_9$, and both peripheral $R^1 = -CH_3$, or

R^2 =  , both non-peripheral $R^1 = -O^nC_5H_{11}$ or $-OC_8H_{17}$, and both peripheral R^1 = $-SC_6H_5$, or

R^2 =  , and all four $R^1 = -CH_2C_6H_5$, or

R^2 =  or  , both non-peripheral $R^1 = -O^nC_4H_9$, and all two or four peripheral R^1 = –H,

R^2 =  , one peripheral R^1 = –Cl or –Br, and all five remaining R^1 = –H, or

R^2 =  , both peripheral $R^1 = -OC_6H_5$, and both non-peripheral $R^1 = H$.

2. The substituted phthalocyanine of claim 1, wherein the substituted phthalocyanine is a non-mixed or a mixed phthalocyanine.

3. The substituted phthalocyanine of claim 1 or claim 2, wherein R^1 are the same or different and each R^1 is C_1-C_{20} alkyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$ and/or $-N(R^5)_3^+$; C_2-C_{20} alkenyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$ and/or $-N(R^5)_3^+$; C_2-C_{20} alkynyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-Si(R^5)_3$, $-C_5H_4N$, $-C_4H_3S$ and/or $-C_6H_5$; $-OR^5$; $-SR^5$; $-SO_2R^5$; $-N-(R^5)_2$; $-P-(R^5)_2$; $-P(O)(OR^5)_2$; –aryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-OR^5$, $-SO_3H$, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$; –heteroaryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$; $-COR^5$; $-COOR^5$; $-CON(R^5)_2$; –F; –Cl; –Br; –I or $-B(OH)_2$; where $-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl, hetereoaryl or H, or two $-R^5$ together form a saturated or unsaturated ring.

4. The substituted phthalocyanine of claim 3, wherein R^1 are the same or different and each R^1 is C_1-C_{20} alkyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$ and/or $-NHR^5$; C_2-C_{20} alkenyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$ and/or $-NHR^5$; C_2-C_{20} alkynyl, optionally substituted with one or more of –F, –Cl, –Br, –I, –OH, $-OR^5$, $-SR^5$, $-NH_2$ and/or $-NHR^5$; $-OR^5$; $-SR^5$; $-SO_2R^5$; $-N-(R^5)_2$; $-P-(R^5)_2$; –aryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-OR^5$, $-SO_3H$, $-NH_2$ and/or $-NHR^5$; –heteroaryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-NH_2$ and/or $-NHR^5$; $-COR^5$; $-COOR^5$; $-CON(R^5)_2$; –F; –Cl; –Br or –I; where $-R^5$ are the

same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl, hetereoaryl or H, or two $-R^5$ together form a saturated or unsaturated ring.

5. The substituted phthalocyanine of claim 1 or claim 2, wherein R^1 are the same or different and each R^1 is C_1-C_{20} alkyl substituted with at least one or more of –F, –Cl, –Br, –I, –OH, $-NH_2$, $-NHR^5$, $-N(R^5)_2$ and/or $-N(R^5)_3^+$; C_2-C_{20} alkenyl; C_2-C_{20} alkynyl; $-S-R^5$; $-N-(R^5)_2$; –aryl, optionally substituted with one or more of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH, $-NH_2$, $-NHR^5$, $-N(R^5)_2$, $-N(R^5)_3^+$, $-NHCOR^5$, $-COR^5$, $-COOR^5$ and/or $-CON(R^5)_2$; –F; –Cl; –Br or –I; where $-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl, heteroaryl or H, or two $-R^5$ together form a saturated or unsaturated ring.

6. The substituted phthalocyanine of claim 5, wherein R^1 are the same or different and each R^1 is C_1-C_{20} alkyl fully substituted with –F, –Cl and/or –Br; C_2-C_{20} alkenyl; C_2-C_{20} alkynyl; $-S-R^5$; –aryl, optionally substituted with one or more of $-CH_3$, $-NO_2$, $-OCH_3$, –F, –Cl, –Br, –OH and/or $-NH_2$; –F; –Cl; –Br or –I; where $-R^5$ are the same or different and each $-R^5$ is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, aryl, heteroaryl or H, or two $-R^5$ together form a saturated or unsaturated ring.

7. The substituted phthalocyanine of any one of claims 1 to 6, wherein at least one R^1 is a non-peripheral substituent.

8. The substituted phthalocyanine of any one of claims 1 to 7, wherein the substituted phthalocyanine of formula (I) is substituted with or conjugated to an amino acid, a fatty acid, a nucleic acid, a di-, tri- or up to decapeptide, a polypeptide, a protein, a saccharide, a polysaccharide or a polymer.

9. The substituted phthalocyanine of claim 8, wherein the substituted phthalocyanine of formula (I) is substituted with or conjugated to an amino acid, a fatty acid, a nucleic acid, a di-, tri- or up to decapeptide, a polypeptide, a protein, a saccharide, a polysaccharide or a polymer via R^1.

10. The substituted phthalocyanine of any one of claims 1 to 9, wherein R^2 is  .

11. The substituted phthalocyanine of any one of claims 1 to 10, wherein m is 1 or 2.

12. The substituted phthalocyanine of any one of claims 1 to 11, wherein $R^1_{n1} = R^1_{n2} =$ $-C_5H_{11}$ or $-C_6H_{13}$, $R^1_{p1} = R^1_{p2} = -H$, and $R^2 =$.

13. The substituted phthalocyanine of any one of claims 1 to 12, wherein the substituted phthalocyanine forms a sandwich complex.

14. The substituted phthalocyanine of any one of claims 1 to 12, wherein the substituted phthalocyanine forms a multimer.

15. The substituted phthalocyanine of claim 14, wherein the multimer comprises at least two phthalocyanines.

16. The substituted phthalocyanine of claim 15, wherein the at least two phthalocyanines forming the multimer are covalently linked.

17. The substituted phthalocyanine of claim 16, wherein the covalently linked phthalocyanines are covalently linked via R^1.

18. The substituted phthalocyanine of any one of claims 1 to 17, wherein the substituted phthalocyanine is conjugated to a carrier, or entrapped or embedded in a carrier.

19. The substituted phthalocyanine of claim 18, wherein the carrier is an amino acid, a fatty acid, a nucleic acid, a di-, tri- or up to decapeptide, a polypeptide, a protein, a saccharide, a polysaccharide or a polymer.

20. The substituted phthalocyanine of claim 18 or claim 19, wherein the substituted phthalocyanine is conjugated to the carrier via R^1.

21. The substituted phthalocyanine of claim 19, wherein the polypeptide is an antibody.

22. The substituted phthalocyanine of claim 18, wherein the substituted phthalocyanine is entrapped or embedded in a solid polymer, or wherein the substituted phthalocyanine is conjugated to a soluble polymer.

23. The substituted phthalocyanine of claim 22, wherein the solid polymer is selected from polyesters, poly(orthoesters), polyanhydrides, tyrosine derived pseudo-poly(amino acids) or polyphosphazenes, or wherein the soluble polymer is selected from N-(2-hydroxypropyl)methacrylamide (HMPA) copolymers, polyvinylpyrrolidone (PVP), poly(ethylene glycol) (PEG) polymers, copolymers or block copolymers, amino acid derived polymers or polyesters.

24. The substituted phthalocyanine of claim 22 or claim 23, wherein the solid or soluble polymer is a biodegradable polymer.

25. The substituted phthalocyanine of any one of claims 1 to 24 for use as a medicament.

26. The substituted phthalocyanine of claim 25, wherein the medicament is for use in the photodynamic therapy of a human or animal disease.

27. The substituted phthalocyanine of claim 25, wherein the medicament is for use in photodiagnostics.

28. A pharmaceutical composition comprising a substituted phthalocyanine according to any one of claims 1 to 27 or a pharmaceutically acceptable salt thereof in a mixture or in association with a pharmaceutically acceptable carrier, diluent or excipient.

29. The pharmaceutical composition of claim 28, wherein the pharmaceutical composition is in a form suitable for topical, subcutaneous, mucosal, parenteral, systemic, intra-articular, intra-venous, intra-muscular, intra-cranial, rectal or oral application.

30. The pharmaceutical composition of claim 28 or claim 29, for use in the photodynamic therapy of a human or animal disease.

31. The pharmaceutical composition of claim 30, wherein the human or animal disease is characterised by benign or malignant cellular hyperproliferation or by areas of neovascularisation.

32. The pharmaceutical composition of claim 30, wherein the human or animal disease is a viral, fungal or bacterial disease or a disease caused by prions.

33. The pharmaceutical composition of claim 30, wherein the human or animal disease is a tumour, rheumatoid arthritis, inflammatory arthritis, hemophilia, osteoarthritis, vascular stenosis, vascular restenosis, atheromas, hyperplasia, intimal hyperplasia, benign prostate hyperplasia, psoriasis, mycosis fungoides, eczema, actinic keratosis or lichen planus.

34. The pharmaceutical composition of claim 28 or claim 29, for use in photodiagnostics.

35. The pharmaceutical composition of claim 28 or claim 29, for use in the inactivation of a microorganism.

36. The pharmaceutical composition of claim 35, wherein the microorganism comprises Gram positive bacteria, Gram negative bacteria, yeasts, fungi, algae or parasites at any stage in their development.

37. A composition comprising a substituted phthalocyanine according to any one of claims 1 to 27 for use in the inactivation of a microorganism.

38. The composition of claim 37, wherein the microorganism comprises Gram positive bacteria, Gram negative bacteria, yeasts, fungi, algae or parasites at any stage in their development.

39. A composition of any one of claims 35 to 38, wherein the inactivation of the microorganism requires illumination.

40. A composition of any one of claims 35 to 38, wherein the inactivation of the microorganism does not require illumination.

41. The composition of any one of claims 30 to 34 or claim 39, wherein the source of illumination is a laser or a non-coherent light source emitting light of optimal wavelength.

42. Use of a substituted phthalocyanine of any one of claims 1 to 27 for the manufacture of a phototherapeutic agent for the use in photodynamic therapy.

43. The use of claim 42, wherein the phototherapeutic agent is used for the treatment of a disease characterised by benign or malignant cellular hyperproliferation.

44. The use of claim 42, wherein the phototherapeutic agent is used for the treatment of a viral, fungal or bacterial disease or a disease caused by prions.

45. The use of claim 42, wherein the phototherapeutic agent is used for the treatment of a disease such as a tumour, rheumatoid arthritis, inflammatory arthritis, hemophilia, osteoarthritis, vascular stenosis, vascular restenosis, atheromas, hyperplasia, intimal hyperplasia, benign prostate hyperplasia, psoriasis, mycosis fungoides, eczema, actinic keratosis and lichen planus.

46. Use of a substituted phthalocyanine of any one of claim 1 to 27 for the manufacture of a photodiagnostic agent for the identification of areas that are pathologically affected by cellular hyperproliferation.

47. A material comprising a substituted phthalocyanine of any one of claims 1 to 27, wherein the optical or physical properties of the material may be altered by incident radiation.

48. The material of claim 47, wherein the incident radiation is electromagnetic radiation.

49. The material of claim 48, wherein the incident radiation is electromagnetic radiation with a wavelength in the range of from 200nm to 1000nm.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02465

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F7/02 A61K31/695 A61P29/02 A61P35/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; VOROZHTSOV, G. N. ET AL: "Phosphonylmethyl phthalocyanine derivatives in preparations for photodynamic therapy" retrieved from STN Database accession no. 136:183942 XP002211842 abstract	1-49
X	-& RU 2 146 144 C (LUK JANETS EVGENIJ ANTONOVICH;TORSHINA NADEZHDA L VOVNA; JUZHAKOVA OL) 10 March 2000 (2000-03-10) the whole document column 9, line 31 -column 10, line 37	1-49

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 September 2002	16/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bader, K

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SONCIN, MARINA ET AL: "Pharmacokinetic and phototherapeutic properties of axially substituted Si(IV)-tetradibenzobarreleno-octabutoxypht halocyanines" JOURNAL OF PHOTOCHEMISTRY AND PHOTOBIOLOGY, B: BIOLOGY (1997), 40(2), 163-167 , XP001104023 page 164; figure 1 ---	1-49
X	BRASSEUR, NICOLE ET AL: "Synthesis and Photodynamic Activities of Silicon 2,3-Naphthalocyanine Derivatives" J. MED. CHEM., vol. 37, no. 3, 1994, pages 415-420, XP001074177 page 416 page 417; figure 2 ---	1-49
X	WO 96 29367 A (BIOSITE DIAGNOSTICS INC) 26 September 1996 (1996-09-26) page 63 -page 86 ---	1-24, 47-49
X	WO 95 08772 A (BIOSITE DIAGNOSTICS INC) 30 March 1995 (1995-03-30) page 35 -page 93 ---	1-24, 47-49
X	JP 06 157536 A (TOYO INK MFG CO LTD) 3 June 1994 (1994-06-03) page 447 ---	1-7, 47-49
X	WO 96 10620 A (EASTMAN CHEM CO) 11 April 1996 (1996-04-11) page 54 -page 66 ---	1-7, 47-49
X	US 5 763 189 A (NOAR J BARRY ET AL) 9 June 1998 (1998-06-09) figures 6,9 ---	1-7, 47-49
X	US 5 824 799 A (NOAR JOSEPH B ET AL) 20 October 1998 (1998-10-20) figures 6,7,9 ---	1-7, 47-49
X	JP 03 071888 A (TOYOBO CO LTD) 27 March 1991 (1991-03-27) the whole document ---	1-7, 47-49

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INTERNATIONAL SEARCH REPORT

tional Application No
PCT/GB 02/02465

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	AOUDIA M ET AL: "Synthesis of a Series of Octabutoxy- and Octabutoxybenzophthalocyani nes and Photophysical Properties of Two Members of the Series" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 119, no. 26, 1997, pages 6029-6039, XP002186613 ISSN: 0002-7863 page 6030 ---	1-7, 47-49
A	WO 98 14521 A (UNIV CLEVELAND HOSPITALS) 9 April 1998 (1998-04-09) cited in the application the whole document ---	1,28,37, 42,46,47
A	WO 92 01753 A (KENNEY MALCOLM E ;OLEINICK NANCY L (US); RIHTER BORIS D (US)) 6 February 1992 (1992-02-06) cited in the application the whole document ---	1,28,37, 42,46,47
P,X	WO 01 90399 A (DADE BEHRING INC) 29 November 2001 (2001-11-29) page 40 ---	1-49
P,X	WO 01 84157 A (DADE BEHRING INC) 8 November 2001 (2001-11-08) page 50 -----	1-49

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/GB 02/02465

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-49 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-49 (all in part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search for the compounds according to claim 1 (M=si; X=-H/-CH3/-CH2CH3)has been restricted to compounds according to the formula on page 96 of the application, in which the compounds are always carrying a substiuent in all positions R1/R3/R5/R7 (see tabloid on pages 97-99) and the silicon containing compounds as specifically disclosed in the publication in the tabloid on pages 97-99. All the other dependent and independent claims have only been searched in as far as relating to such compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02465

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Snyder, Joseph R.

From: ddraney@licor.com
Sent: Friday, September 05, 2003 2:53 PM
To: Snyder, Joseph R.
Cc: xpeng@licor.com; kpetersen@licor.com
Subject: Re: 020031-002700 Update to Provisional

Hi Joe,

The attached document has some supplemental material regarding the 750 dye for possible inclusion in the full application. It is mainly in the form of diagrams, but has some text. We are now very close to making the 750 dye. I also made some comments in the document, using Word's comments feature. In particular I have tried to clearly indicate what has already been accomplished vs. what is prophetic.

One 750 difference from the original plan is the use of S for the link to the dye ring rather than O. Also, instead of OCH3 groups around the rings we are using OCH2CH2OCH3 groups. The broad claims should cover these differences already, but specific 750 dye claims should be revised.

With respect to the 680 dye as originally described and claimed, the past year has brought some more info. Ultimately we settled on a slightly different structure from the primary one at the original filing. The difference is only two extra methylene groups in the linker part of the molecule, so it is a very small difference. The advantage is the NHS ester is a bit less reactive than with the shorter linker. We did not redo the original diagrams to reflect this difference, but the 750 diagram shows the longer linker. We should probably update the claims to include the specific structure with the new linker.

We have done considerable work improving the process for making the 680 dye over the past year. The conditions and yields in the provisional could be revised in light of this work, but we have not done so yet. Since the details of the synthetic steps were not described originally, we have not provided the new synthetic details. Should we do that?

Since the filing there have also been more applications testing of the Pc680 dye, including: use of labeled antibodies for Western blots and "In Cell Western" analyses; fluorescence polarization; and FRET with other dyes. This application data has not been provided to you, but we can do so if needed to strengthen the application. In our previous discussions we decided not to include new claims for FRET or FP with the dyes of the invention.

Xinzhan identified some particular spots in the original application where it seems some new stuff could be needed.

1. Perhaps between [0019] and [0020] another preferred embodiment with alkylthio linkage for "L" and six optional substituted alkoxy groups for R12, R15, R16, R19, R20, and R23.
2. Similar insertion around [0116]
3. Figure Ic [0120] shows the original Pc680 dye, with 3 methylenes between amide and NHS ester. As noted, we now use 5 methylenes, so we probably should change this figure (no new one supplied yet, but we can do so).
4. Claims 12, 13, 27, 28 (specific 750 dye) should be revised to cover the new structure and it's isomer (postion of linkage)

You can decide how to introduce the new material in the spec, as you are the expert.

Best,
Dan